Efforts at Expanding the Scope of Peptides as Enantioselective Organic Catalysts

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Abstract

The development of peptides as catalysts for preparing optically active molecules is an ongoing investigation. Efforts at expanding the use of peptides are explored in two ways: investigating novel reactions in which peptides can act as asymmetric catalysts and through expanding the substrate scope of peptides in performing kinetic resolutions.

Attempts at furthering the reaction scope of acylsulfonamide-containing peptides to act as Brønsted acids through promoting the attack of 7-methyl oct-6-ene-1-tosylaziridine (**9**) by an internal π-nucleophile are discussed herein. Also reported is the use of pentameric peptides containing a π(-methyl)histidine residue in the kinetic resolution of the primary alcohol 4-hydroxymethyl cyclopent-2-enone (**76**) and the secondary aliphatic alcohol 2-pentanol. Moderate selectivities were observed in the kinetic resolution of 4-hydroxymethyl cyclopent-2-enone (**76**) and promising results were obtained in the initial screening of catalysts for the resolution of 2-pentanol.

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3. Kinetic resolution of aliphatic alcohols

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I would also like to express my undying gratitude to my parents, grandparents, brother and sister. Without their wisdom, moral support, or inspiration I would surely be lost.

Introduction

Molecular recognition is a powerful concept in organic chemistry. The idea of non-covalent interactions is not new and is at the heart of many chemical interactions, especially between a catalyst and substrate. Understanding and utilizing these interactions provides a great and yet unmet challenge in the development of organic chemistry. While there is a considerable amount known about the different types of interactions concerning both attractive forces such as hydrogen bonding or repulsive forces such as electrostatic repulsion, harnessing the power of such effects is still a developing concept.[1] Designing and implementing organocatalysts is arguably one of the most interesting applications implied in studying non-covalent interactions. Progress in this area has been staggering in recent years, leading to a plethora of reactions in which organocatalysis can now be implemented.[2]

Using some of the fundamentals of molecular recognition, the Miller laboratory has developed peptide catalysts that perform a variety of reactions, including asymmetric phosphorylation and acylation. These peptide catalysts have successfully demonstrated effectiveness in performing kinetic resolutions of several secondary and tertiary alcohols along with the desymmetrization of a primary diol. It is thought that hydrogen bonding contributes to the selectivity of these reactions in two ways: (1) by controlling the peptide secondary structure; and (2) through stabilizing interactions between the catalyst and substrate.[3]

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[1] (a) For a compendium of reviews on molecular recognition see: *Chem. Rev*. **1997**, *97*. (b) Gellman, S. H. *Chem. Rev.*, **1997**, *97*, 1231-1232.
[2] Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138-5175. (b) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2001**, *40*, 3726-3748.
[3] Jarvo, E. R.; Copeland, G. T.; Papaioannou, N.; Bonitatebus, P. J. Jr.; Miller, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11638-11643.

Expanding the use of peptides as enantioselective catalysts is an ongoing effort. Experiments dealing with the diversification of the reaction and substrate scope for peptides in preparing optically active compounds are reported herein. Research was focused on performing kinetic resolutions of the primary alcohol 4-hydroxymethyl cylclopent-2-enone (**76**) and the aliphatic secondary alcohol 2-pentanol. In addition, attempts at utilizing peptides containing acylsulfonamides as Brønsted acid catalysts were also investigated in promoting the nucleophilic attack on a *p*-tolunesulfonyl protected aziridine **9** from an internal π-nucleophile.

Chapter 1: π-Nucleophilic Attack on Aziridines Promoted by BrØnsted Acids

1.1 BrØnsted Acids as Organocatalysts

The ability of Brønsted acids to perform as organic catalysts has been historically well documented; however, until recently they have generally been underutilized in organic synthesis.[4] Brønsted acids as asymmetric catalysts have been largely overshadowed by Lewis acids for a variety of reasons, including the capability of "tuning" steric and electronic characteristics around a metal center by adjusting attached ligands or counter ions. Another disadvantage associated with Brønsted acid catalysis is the lack of directionality associated with the hydrogen atom's s orbital.[5] Despite initial prejudice towards Brønsted acids their utility as asymmetric catalysts has reemerged as an area of increased interest. The use of Brønsted acids as catalysts has recently been reported for a variety of transformations including the Diels-Alder reaction, Michael additions, the Strecker reaction, the Morita Baylis-Hillman reaction, and in the hydrogenation of imines.[6]

Jacobsen applied thiourea based catalysts to the asymmetric Strecker reaction in his seminal work on Brønsted acids as organocatalysts.[7] In an investigation involving thioureas

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[4] (a) Babine, R. E.; Bender, S. L. *Chem. Rev.* **1997**, *97*, 1359-1472. (b) Schmidtchen, F. P.; Berger, M. *Chem. Rev.* **1997**, *97*, 1609-1646.

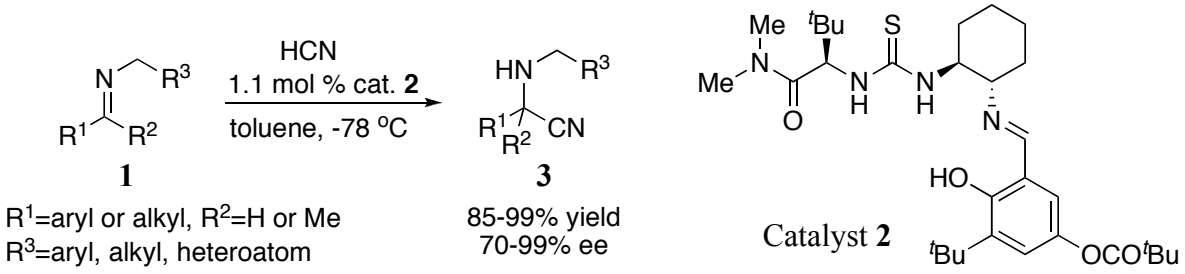
[5] (a) Taylor M. S.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2006**, *45*, 1520-1543. (b) Connon, S. J. *Angew. Chem. Int. Ed.* **2006**, *45*, 3909-3912.

[6] For examples see: (a) Schreiner, P. R.; Wittkopp, *Org. Lett.* **2002**, *4*, 217-220. (b) Rueping, M.; Azap, C.; Sugiono, E.; Theissmann, T. *Synlett* **2005**, *15*, 2367-2369. (c) Schuster, T.; Bauch, M.; Durner, G.; Gobel, M. W. *Org. Lett.* **2000**, *2*, 179-181. (d) Huang, Y.; Unni, A. K.; Thadani, A. N.; Rawal, V. H. *Nature* **2003**, *424*, 146. (e) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003,** *125*, 12672-12673.

[7] (a) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 5315-5316. (b) Sigman, M. S.; Vachal, P.; Jacobsen E. N. *Angew. Chem. Int. Ed.* **2000**, *39*, 1279-1281. (c) Vachal, P.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 867-870. (d) Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002,** *124*, 10012-10014.

as ligands for metal catalyst control, experiments revealed that the ligand was a competent catalyst for the addition of cyanide to imine substrates. A detailed investigation into the mechanism of this reaction indicates a hydrogen bond interaction between thiourea catalyst **2** and imine **1** (Scheme 1). This hydrogen bond is thought to activate the imine towards nucleophilic attack from cyanide. Additionally the hydrogen bond likely influences the selective outcome of this reaction by helping to maintain a rigid transition state. Although all of the details of this mechanism are not fully elucidated, the Jacobsen group has demonstrated that this catalyst can be applied to a variety of substrates, resulting in excellent selectivity and yields (Scheme 1).

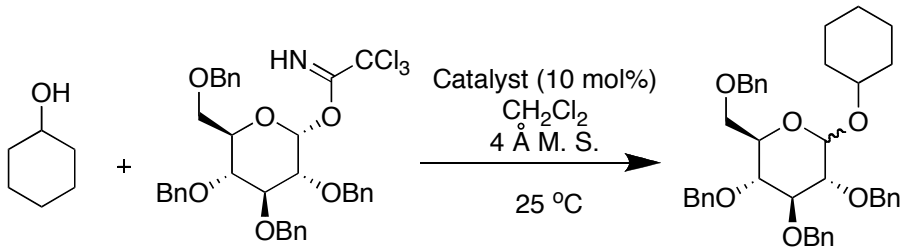
Scheme 1: Asymmetric Strecker reaction using Jacobsen's thiourea catalsyt



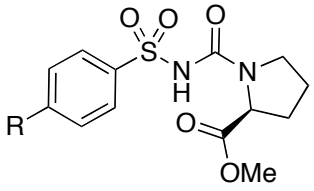
Investigation into novel methods for catalyzing regiospecific glycosylation reactions led to initial interest in Brønsted acids as catalysts. Through activation of sugar **5**, and presumably oxonium ion formation, partial selectivity is observed relating to formation of α to β anomers.[8] Using the achiral Brønsted acid catalyst picric acid, this reaction results in a 3:2 ratio of the α to β anomers. With the use of acylsulfonamide catalyst **2** a 2:3 ratio of products is observed, with the opposite anomer being the major product (Scheme 2).

[8] Griswold, K. S.; Horstmann, T. E.; Miller, S. J. *Synlett* **2003**, *12*, 1923-1926.

Scheme 2: Acid activation of trichloroacetimidate



4 **5** **6**

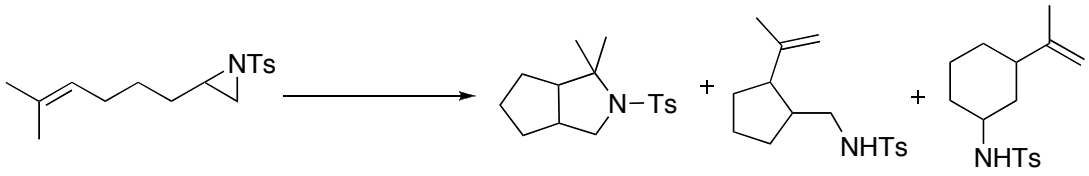


catalyst **7**
A: R=CH_3
B: R=Cl

Cat.	Reaction time (h)	Yield (%)	α/β
picric acid	1.5	Quant.	60:40
7A	43	60	40:60
7B	24	80	40:60

In an effort to examine the prowess of acylsulfonamides as Brønsted acids, an investigation focused on the activation of aziridines towards intramolecular attack from π-nucleophiles was undertaken. To study this possibility it was decided to focus on the cyclization of 7-methyl octa-6-ene-1-tosylaziridine (**8**). It was envisaged that a Brønsted acid catalyst could be utilized to promote the cyclization of aziridine **8**, resulting in the formation of three distinct products (Scheme 3). Further, utilizing a chiral Brønsted acid would open the possibility of selectively controlling the product ratio and provide a means to obtain optically active products by way of a kinetic resolution of the racemic starting material.

Scheme 3: Cyclization of 7-methyl oct-6-ene-1-tosylaziridine (**8**)



8 **9** **10** **11**

1.2 Aziridines in Organic Chemistry

Aziridines possess unique and fascinating reactivity due to a high ring strain energy of 27-28 kcal mol^{-1}. This ring strain is mostly a result of restricted bond angles (60^{o}) necessary for the formation of a three-membered ring. Chemists have taken advantage of this reactivity and by utilizing aziridines in a variety of different situations: as intermediates in the synthesis of small molecules, chiral auxilaries for controlling selectivity and as monomeric units in the formation of polymers. [9]

The strain associated with a three-membered ring leaves aziridines susceptible towards attack from a variety of nucleophiles including nitrogens, oxygens, phosphines and carbons (Scheme 4a).[10] Activation of aziridines can also be achieved through ring opening, with stabilization of the resulting 1,3 dipole, allowing formal [3+2] cycloaddition reactions to occur with a variety of olefins (Scheme 4b).[11] Reduction of aziridines via a one electron transfer process using samarium iodide has allowed for the synthesis of a variety of β-amino ketones (Scheme 4c).[12] Aziridines also present themselves as precursors in chemical synthesis that can readily undergo ring expansion, giving a variety of products, including β-lactams (Scheme 4d).[13,14]

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[9] For a comprehensive review on Aziridines see: Pearson, W. H.; Lian, B. N.; Bergmeier, S. C. *Comprehensive Heterocyclic Chemistry II*, ed. A. R. Katritzky, C. W. Ress, E. F. Scriven and A. Padwa, Pergamon, Oxford, 1996, **Vol. 1A**, p. 1-60.

[10] Wakamiya, T.; Shimbo, K.; Shiba, T.; Nakajima, K.; Neya, M.; Okawa, K. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3878-3881.

[11] Garner, P.; Dogan, O.; Youngs, W. J.; Kennedy, V. O.; Protasiewicz, J.; Zaniewsjki, R. *Tetrahedron* **2001**, *57*, 71-85.

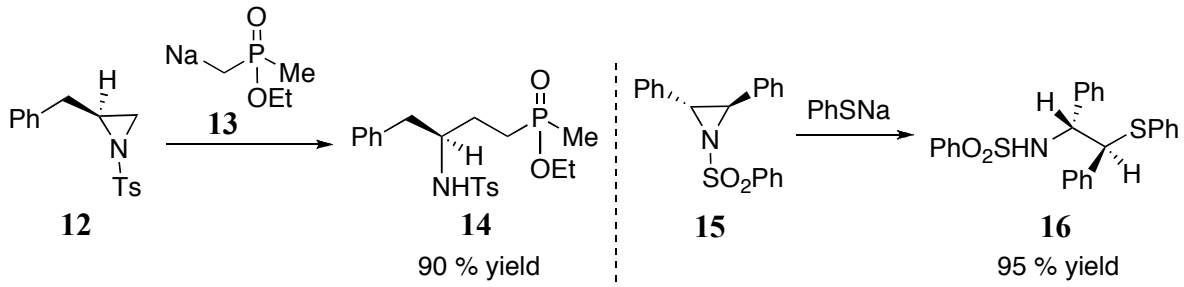
[12] (a) Molander, G. A.; Stengel, P. J. *J. Org. Chem.* **1995**, *36*, 8431. (b) Molander, G. A.; Stengel, P. J. *Tetrahedron* **1997**, *53*, 8887-8912.

[13] (a) Fugami, K.; Miura, K.; Morizawa, Y.; Oshima, K.; Utimoto, K.; Nozaki, H. *Tetrahedron* **1989,** *45*, 3089-3098. (b) Spears, G. W.; Nakanishi, K.; Ohfune, Y. *Synlett* **1991**, 91-92 (c) Chamchaang, W.; Pinhas, A. R. *J. Org. Chem.* **1990**, *55*, 2943-2950.

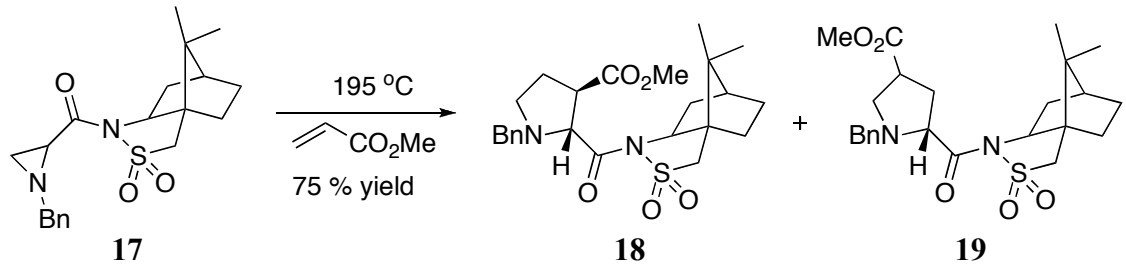
[14] Tanner, D. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 599-619.

Scheme 4: Reactions of aziridines

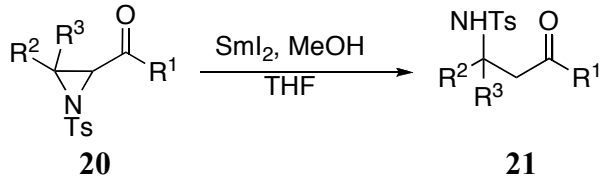
A: Nucleophilic attack of aziridines



B: 1,3 dipolar cycloaddition

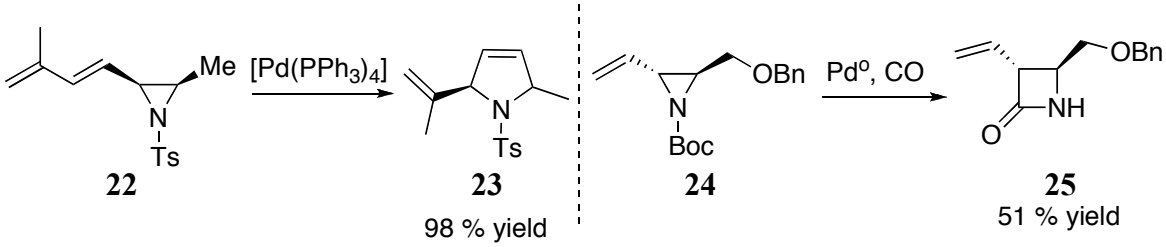


C: Reduction of aziridines



Aziridine	Yield
a R^1=Me, R^3=Ph	87
b R^1=Me	95
c R^1=Me, R^2, R^3=Me	78
d R^1,R^2=$(CH_2)_3$	87

D: Ring expansion of aziridines

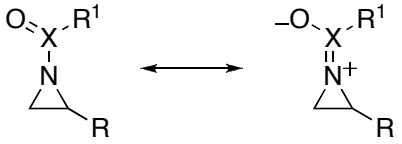


Protected nitrogens in aziridines show different physical characteristics than aliphatic nitrogens. Due to the strain associated with aziridines, more sp^3 character at the nitrogen is observed, instead of the expected sp^2 character of a sulfonamide. Because of this skewed

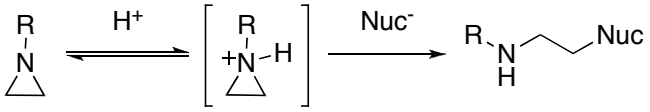
hybridization, the orbital containing the lone pair of electrons on the nitrogen possesses more S character than would be expected. As a result of the nitrogen's lone pair's greater S character, carbonyl or sulfonyl protecting groups contain less iminium character than observed in less strained systems.[15]

Figure 1: reactivity of Aziridines

A) Resonance of aziridines



B.) Protonation of Aziridines



1.3 π-Nucleophilic Attack on Aziridine Rings: Previous Examples

Reactivity of azridines towards nucleophilic attack provides interesting avenues for organic synthesis. Exploiting this reactivity provides novel methodology in the production of optically active synthetic intermediates. While it is necessary to establish the stereochemistry in the initial preparation of the aziridine ring to achieve optically active products, there are still issues of regioselectivity that merit consideration in the nucleophilic attack of aziridines. Of particular interest is the ability of π-based nucleophiles to attack aziridines, resulting in a new carbon-carbon bond, or substituted ring systems in the case of an internal π-nucleophile.

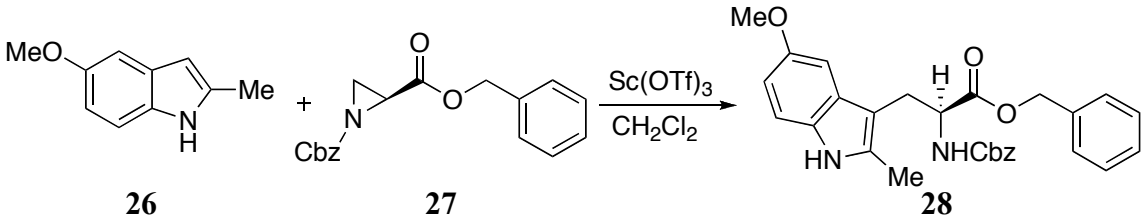
Early examples of π-nucleophilic attack on aziridines employ the use of Lewis acid catalysts with indole or pyrrole as the π-nucleophile.[16] An example of this work includes the

[15] McCoull, W.; Davis, F. A. *Synthesis* **2000**, *10*, 1347-1365.
[16] (a) Nishikawa, T.; Kajii, S.; Wada, K.; Ishikawa, M.; Isobe, M. *Synthesis* **2002**, *12*, 1658-1662. (b) Sato, K.; Kozikowski, A. P. *Tetrahedron Lett.* **1989**, *30*, 4073-4076.

use of scandium triflate to prepare tryptophan derivatives **28** (Scheme 5A).[17] Similarly, indium tribromide has been shown to be as an effective Lewis acid in activating aziridines towards the attack from pyrrole **30** (Scheme 5B).[18]

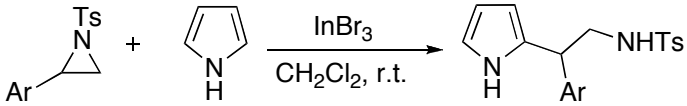
Scheme 5: Lewis acid activation of aziridines

A: Preparation of tryptophan analogs



26 **27** **28**

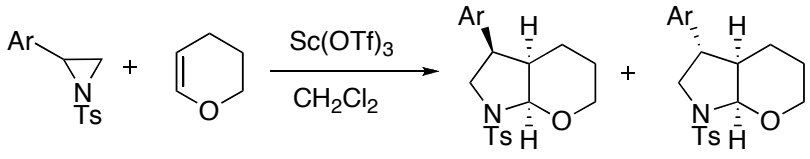
B: Indium promoted attack of aziridines by pyrrole



29 **30** **31**

Aziridines also participate in formal [3+2] cycloadditions. These cyclizations have been reported to be catalyzed by a variety of Lewis acids. As demonstrated by Ungureanu *et al.,* treatment of aziridine **29** with scandium triflate in the presence of furan **32** leads to bicyclic products **33a** and **33b** (Scheme 6).[19]

Scheme 6: Formal [3+2] cycloaddition of aziridines and alkenes

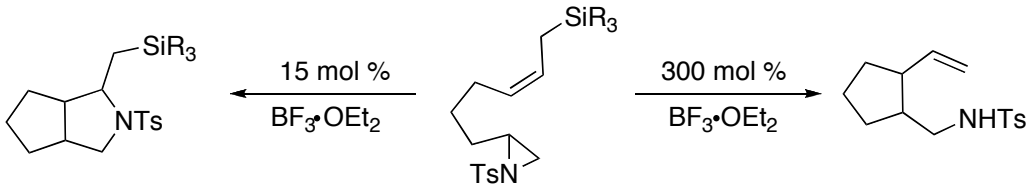


29 **32** **33a** **33b**

[17] Bennani, Y. L.; Zhu, G.-D.; Freeman, J. C. *Synlett* **1998**, 754-756.
[18] (a) Yadav, J. S.; Reddy, B. V. S.; Parimala, G *Synlett* **2002**, 1143-1145. (b) Yadav, J. S.; Reddy, B. V. S.; Abraham, S.; Sabitha, G. *Tetrahedron Lett.* **2002**, *43*, 1565-1567.
[19] (a) Ungureanu, I.; Bologa, C.; Chayer, S.; Mann, A. *Tetrahedron Lett.* **1999**, *40*, 5315-5318. (b) Yadav, J. S.; Reddy, B. V. S.; Pandey, S. K.; Srihari, P.; Prathap, I. *Tetrahedron Lett.* **2001**, *42*, 9089-9092.

In 1999, Bergmeier *et al.* demonstrated the importance that the stoichiometry of the Lewis acid plays on the reaction outcome. Treatment of aziridine **34** with a catalytic amount of BF_3•OEt_2 gave bicyclic pyrrolidine product **35**, resulting from a formal [3+2] cyclization between the 1,3-dipole and the olefin. When that same aziridine is subjected to a superstoichiometric amount of BF_3•OEt_2, the monocyclic product resulting form the π-nucleophilic attack of the alkene is observed (Scheme 7). While this is an intriguing outcome, there is no explanation offered as to the alteration of the reaction mechanism resulting from the differing amounts of Lewis acid used.[20]

Scheme 7: Effects of Lewis acid stoichiometry



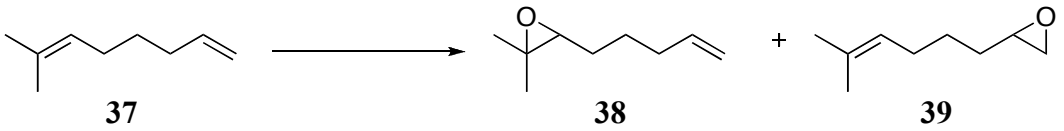
35 **34** **36**

1.4 Preparation of 7-Methyl oct-6-ene-1-tosylaziridine (8)

Preliminary attention to the preparation of 7-methyl oct-6-ene-1-tosylaziridine (**8**) focused on the preparation of 2-(5-methylhex-4-enyl)oxirane (**39**) as a synthetic precursor. With this strategy in mind, epoxidation of 7-methylocta-1,6-diene (**37**) was attempted. Treatment of diene **37** with *m*-CPBA gave exclusively the more substituted epoxide **38** (Scheme 8). This outcome can be rationalized, as the higher substitution of the tertiary olefin increases its electron density, therefore increasing its reactivity towards the electrophilic epoxidation reagent.

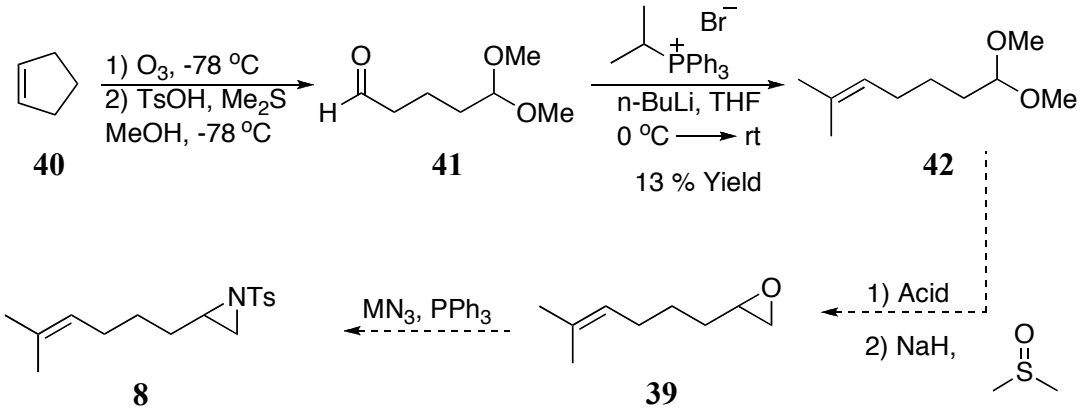
[20] Bergmeier, S. C.; Fundy, S. L.; Seth, P. P. *Tetrahedron* **1999**, *55*, 8025-8038.

Scheme 8: Epoxidation of 7-methylocta-1,6-diene



The second-generation method started with ozonolysis of cyclopentene **40**, using the protocol developed by Schreiber and coworkers, affording dimethyl acetal **41**.[21] Wittig olefination of the resulting aldehyde then gave the desired substituted olefin **42**. It was then envisaged that cleavage of dimethyl acetal **41** with acid would afford the desired aldehyde, which could be treated with dimethyl sulfoxide under Corey-Chaykovsky conditions giving terminal epoxide **44** (Scheme 9).[22] Unfortunately, the volatility of aldehyde **41** coupled with low yields of the Wittig olefination resulted in poor yields for olefin **42**.

Scheme 9: Initial attempt at the preparation of the aziridine

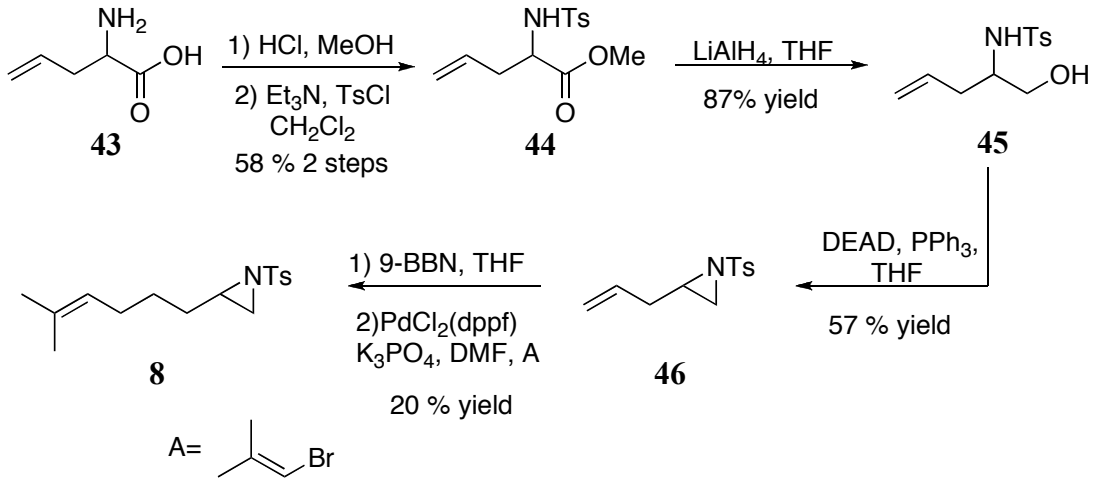


The preparation of 7-methyl oct-6-ene-1-tosylaziridine (**8**) was achieved using a five-step synthesis, starting from racemic allyl glycine **43**. This procedure, originally reported by

[21] (a) Claus, R. E.; Schreiber, S. L. *Org. Synth.* **1986**, *64*, 150-155. (b) Schreiber, S. L.; Kelly, S. E.; Porco, J. A. Jr.; Sammakia, T.; Suh, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 6210-6218.
[22] (a) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1962**, *84*, 866-867. (b) Gololobov, Y. G.; Nesmeyanov, A. N.; Lysenko, V. P.; Boldeskul, I. E. *Tetrahedron* **1987**, *43*, 2609-2651.

Bergmeierer *et al.,* starts with the formation of tosyl amide **44**.[23] Reduction of the methyl ester **44** with lithium aluminum hydride ($LiAlH_4$) gives the desired amino alcohol **45**. Subjection of **45** to Mitsunobu conditions (diethyl azodicarboxylate (DEAD) and triphenyl phosphine (PPh_3)), allows for cyclization giving aziridine **46** in 53% yield. Finally a β-alkyl Suzuki reaction was used to install the desired olefin, giving the final product in five steps (Scheme 10).

Scheme 10: Preparation of aziridine substrate



The first two steps of this synthesis proceeded cleanly giving pure material in excellent yields. However, trouble was encountered when reducing methyl ester **44**. Following literature precedent, sodium borohydride ($NaBH_4$) was originally utilized as the reducing agent, leading to only a moderate yield. To increase the efficiency of this reaction, a variety of reducing agents and work up procedures were examined. Lithium aluminum hydride ($LiAlH_4$) was found to be the most efficient reducing agent. A large boost in yield

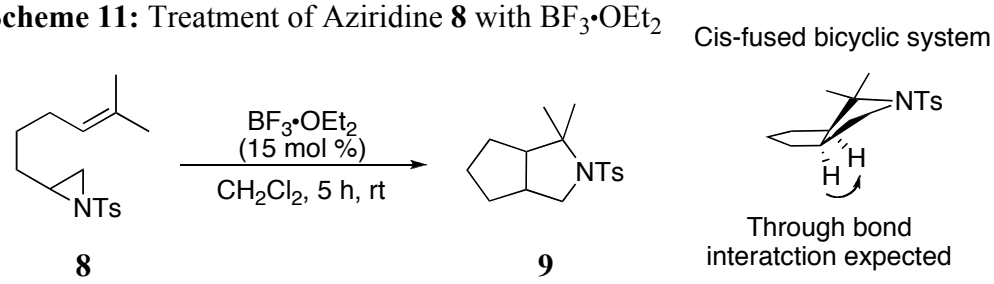
[23] Lapinsky, D. J.; Bergmeier, S. C. *Tetrahedron Lett*. **2001**, 42, 8583-8586.

was also obsereved by altering the work up protocol to involve the addition of water, then 3 molar HCl, followed by more water.[24]

1.5 Results and Discussion

Treatment of 7-methyl oct-6-ene-1-tosylaziridine (**8**) with BF_3•OEt_2, following literature precedent, gave the expected bicyclic pyrrolidine product **9** (Scheme 11). This product was observed as a single diastereomer; however, attempts at elucidating the relative stereochemistry of this product with COSY NMR experiments resulted in no conclusive evidence as to the ring stereochemistry. Due to the large ring strain associated with *trans*-fused bicyclic pyrrolidine rings, it is assumed that the product results from a *cis*-fused bicyclic pyrrolidine ring.

Scheme 11: Treatment of Aziridine **8** with BF_3•OEt_2



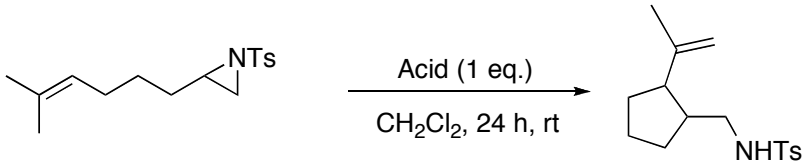
8 **9**

Efforts at probing the reactivity of aziridine **8** with a variety of Brønsted acids leads to the conclusion that a strong acid is necessary to invoke cyclization. Preliminary acids chosen for this study involved catechol, 4,5-dicyanoimidazole, acetic acid, and trifluoroacetic acid (Table 1). These acids were chosen to give a range of pKa's and were tested in both stoichiometric and substoichiometric amounts. Monitoring of each reaction was done using thin layer chromatography and each reaction was run at room temperature. From this initial

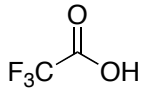
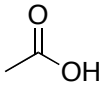
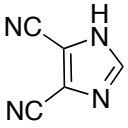
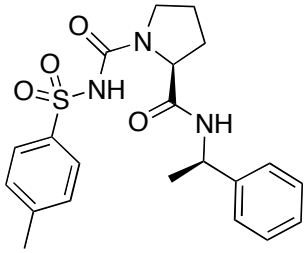
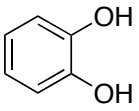
[24] Oi, R.; Sharpless, K. B. *Org. Synth.* **1998**, *9*, 251-257.

study the only acid effective in cyclizing aziridine **8** was trifluoroacetic acid, giving three distinct products.

Table 1: Activation of aziridine by Bronsted Acid



8 **10**

entry	Acid	pKa	Reaction
1		-0.25	3 products
2		4.76	No Reaction
3		5	No Reaction
4		6-7	No Reaction
5		9.48	No Reaction

1.6 Conclusion

As expected from the outcome of previous experiments, treatment of aziridne **8** with both catalytic and stoichiometric amounts of acyl sulfonamide catalyst gave no reaction. This preliminary data indicates that the strength of the acid needed to invoke cyclization is beyond that which acyl sulfonamide provides. Initial limits of the reaction have been identified as being outside the realm of our current technology using peptide catalysis. Strengthening the

acidity associated with acyl sulfonamide by replacing the toluene methyl with a chlorine or a nitro group is a potential solution to this problem. Work involving the use of strong acids in peptides would present some fascinating questions and is an area worthy of further investigation.

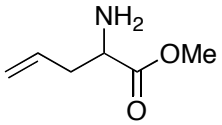
1.7 Experimental

General methods:

^{1}H NMR spectra were recorded on Varian 400 or 300 spectrometers. Proton chemical shifts are reported in ppm (δ) relative to internal tetramethylsilane (TMS, δ 0.0) or with solvent reference relative to TMS employed as the internal standard ($CDCl_3$, δ 7.26 ppm; D_2O, d). Data are reported as follows: chemical shift (multiplicity [singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m)], coupling constants [Hz], integration), ^{13}C NMR spectra were recorded on Varian 400 (100 MHz) or 300 (75 MHz) spectrometers with complete proton decoupling. Carbon chemical shifts are reported in ppm (δ) relative to TMS with the respective solvent resonance as the internal standard ($CDCl_3$, δ 77.0). NMR data were collected at ambient temperature, unless otherwise indicated. In cases where more than one conformation for a given compound is observed at the indicated temperature, the data for the major conformer are reported. Analytical thin-layer chromatography (TLC) was preformed using Silica Gel 60 F254 precoated plates (0.25 mm thickness). Visualization was accomplished by irradiation with UV lamp and/or staining with $KMnO_4$ or Cerium ammonium molybdate (CAM) solutions. Flash column chromatography was preformed using Silica Gel 60A (170-400 mesh) from Fisher Scientific.[25] Mass spectra were obtained at the Mass Spectrometry Facilities of Boston College. All reactions were carried out under a nitrogen atmosphere employing oven- and flame dried glassware. All solvents were distilled from appropriate drying agents or obtained from passing through activated alumina prior to use.

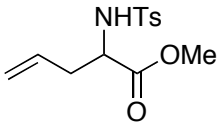
[25] Still, W. C.; Kahn, M.; Mitra, J. *J. Org. Chem.* **1978**, *43*, 2923-2925.

Allyl glycine methyl ester:



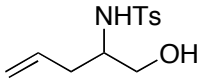
Allyl glycine (**43**) (4 g, 34.8 mmol) was stirred in MeOH (100 mL), HCl was bubbled through the reaction vessel for 2 hours. The reaction vessel was then sealed and allowed to stir overnight at room temperature. The solvent was removed *in vacuo* and azeotroped with toluene giving a white crystalline solid. This solid was carried onto the next step with no further purification. Exact mass calcd. for $[C_{12}H_{17}NO_3SNa]+$ requires *m/z* 278.08 Found 278.02 (ESI+); ^{1}H NMR (D_2O, 400 MHz) 5.72-5.83 (m, 1H), 5.29-5.34 (m, 2H), 4.26 (t, *J*=8 Hz, 1H), 3.86 (s, 3H), 2.65-2.82 (m, 2H) ppm.

Methyl 2-(4-methylphenylsulfonamido)pent-4-enoate (**44**):



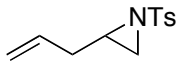
Allyl glycine methyl ester HCl was suspended in methylene chloride (5.7 mL). To this was added *p*-toluenesulfonyl chloride (0.362 g, 1.9 mmol) and triethylamine (0.593 mL, 4.25 mmol). The reaction was allowed to stir at room temperature for 20 hours. The reaction was then washed with water and citric acid (0.5 M). Removal of the solvent *in vacuo* gave a crude brown oil. This oil was purified via flash column chromatography (10%-25% EtOAc/hexanes) giving a clear oil. (0.293 g, 1.0 mmol, 59% two steps); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.72 (d, *J*=8 Hz, 2H), 7.30 (d, J=12 Hz, 2H), 5.57-5.68 (m, 1H), 5.10-5.13 (m, 3H), 4.01-4.06 (m, 1H), 3.52 (s, 3H), 2.47 (t, *J*=6 Hz, 2H), 2.42 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 129.8, 128.1, 124.0, 40.7, 34.2, 31.2, 27.7, 27.3, 26.1, 22.0 ppm.

N-(1-hydroxypent-4-en-2-yl)-4-methylbenzenesulfonamide (**45**):



Lithium aluminum hydride (4 g, 105.5 mmol) was suspended in THF (40 mL) and cooled to 0 ^{o}C (ice bath). The *N*-tosyl allylglycine methyl ester **44** (5.98 g, 21.1 mmol) was dissolved in THF (30 mL) and added to the solution of lithium aluminum hydride ($LiAlH_4$) dropwise via cannula. The reaction was allowed to warm to room temperature upon complete addition of the methyl ester, and stirred at room temperature for 24 hours. The reaction was then cooled to 0 ^{o}C and quenched with water until bubbling ceased. HCl (15 mL, 3 M) was added and followed by the addition of water causing the precipitation of a grey solid. The solid was then filtered and washed with ethyl acetate. Removal of the solvent in vacuo gave an off-white powder. This powder was purified via flash column chromatography (20%-50% ethyl acetate/hexanes) giving a white crystalline solid (4.65 g, 18.3 mmol, 87% yield); Exact mass calcd for $[C_{12}H_{17}NO_3SNa]+$ requires *m/z* 278.08 Found 278.02 (ESI+); ^{1}H NMR ($CDCl_3$, 400 MHz) 7.22 (d, *J*=12 Hz, 2H), 7.29 (d, *J*=12, 2H), 5.57-5.70 (m, 1H), 5.05-5.15 (m, 3H), 3.92-4.03 (m, 2H), 2.46 (t, *J*=8 Hz, 2H), 2.41 (s, 3H), 1.12 (t, *J*= 8 Hz, 2H) ppm.

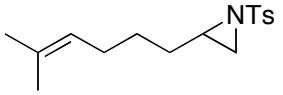
2-allyl-1-tosylaziridine (**46**):



To a mixture of amino alcohol **45** (0.148 g, 0.58 mmol) and triphenyl phosphine (0.184 g, 0.70 mmol) in THF (1.5 mL) was added diethyl azodicarboxylate (DEAD) (0.109 mL, 0.70 mmol). The mixture was allowed to stir at room temperature for 24 hours. Removal of the solvent *in vacuo* gave a crude yellow oil. This oil was purified via flash column chromatography (10%-20% ethyl acetate/hexanes). Fractions

containing product were combined and the solvent removed *in vacuo* to give a yellow oil. (0.078g, 0.33 mmol, 57 % yield); Exact mass calcd for $[C_{12}H_{15}NO_2SNa]+$ requires *m/z* 260.07 Found 260.07 (ESI+); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.82 (d, *J*=8 Hz, 2H), 7.34 (d, *J*=12 Hz, 2H), 5.56-5.66 (m, 1H), 4.97-5.10 (m, 2H), 2.75-2.83 (m, 1H), 2.64 (d, *J*=8 Hz, 1H), 2.45 (s, 3H), 2.14-2.30 (m, 2H), 2.10 (d, *J*=4 Hz, 1H) ppm.

7-methyl oct-6-ene-1-tosylaziridine (**8**):

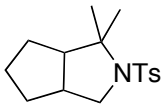


To a 0 °C stirred solution of aziridine **46** (0.386g, 1.63 mmol) in THF (16 mL) was added 9-borabicyclo[3.3.1.]nonane (9-BBN) (0.293g, 2.4 mmol)[26]. The reaction was allowed to warm to room temperature and stirred for 3 hours. DMF was added followed by the dropwise addition of K_3PO_4 (1.1 mL, 3 M, degassed) and the rapid addition of 1-bromo-2-methyl propane (0.184 mL, 1.8 mmol) and $PdCl_2$(dppf) (0.065g, 0.08 mmol). The reaction was stirred at room temperature for 24 hours. The THF was removed in vacuo and the DMF was partitioned between diethyl ether and $NaHCO_3$ (Sat.). The aqueous layer was then extracted with ether and the combined organic layers were dried over magnesium sulfate. Removal of the solvent *in vacuo* gave a crude yellow oil. This oil was purified via flash column chromatography (5%-10% ethyl acetate/hexanes). Fractions containing product were combined and the solvent was removed in vaccuo giving a yellow oil. (0.097g, 0.33mmol, 20 % yield); TLC R_f .46 (20% EtOAc/hexanes); Exact mass calcd for $[C_{16}H_{23}NO_2SK]+$ requires *m/z* 332.11. Found 333.18 (ESI+); IR (film, cm^{-1}) 3547, 2924, 2867, 1596, 1451, 1331, 1168, 1092, 928, 815, 721; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.88 (d, *J*=12 Hz, 2H), 7.39 (d, *J*=12 Hz, 2H), 5.04 (t, *J*=8 Hz,

[26] Soderquist, J. A.; Negron A. *Org. Synth.* **1998**, *9*, 95.

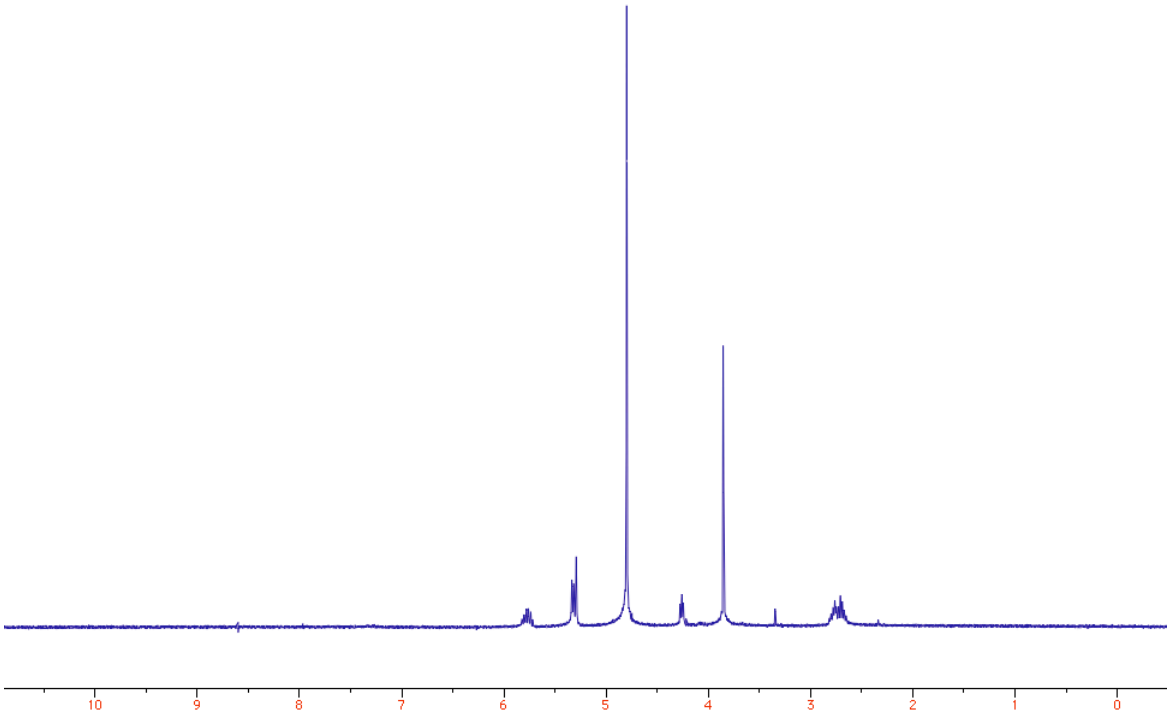
1H), 2.66 (t, *J*=4 Hz, 1H), 2.55 (d, *J*=8 Hz, 1H), 2.36 (s, 3H), 1.97 (d, *J*=4 Hz, 1H), 1.86 (q, *J*=8 Hz, 2H), 1.58 (s, 3H), 1.47 (s, 3H), 1.23 (q, *J*=8 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 130.0, 128.0, 124.0, 40.7, 34.2, 31.2, 27.7, 27.3, 26.1, 22.0, 18.1 ppm.

1,1-dimethyl-2-tosyloctahydrocyclopenta[c]pyrrole (**9**):

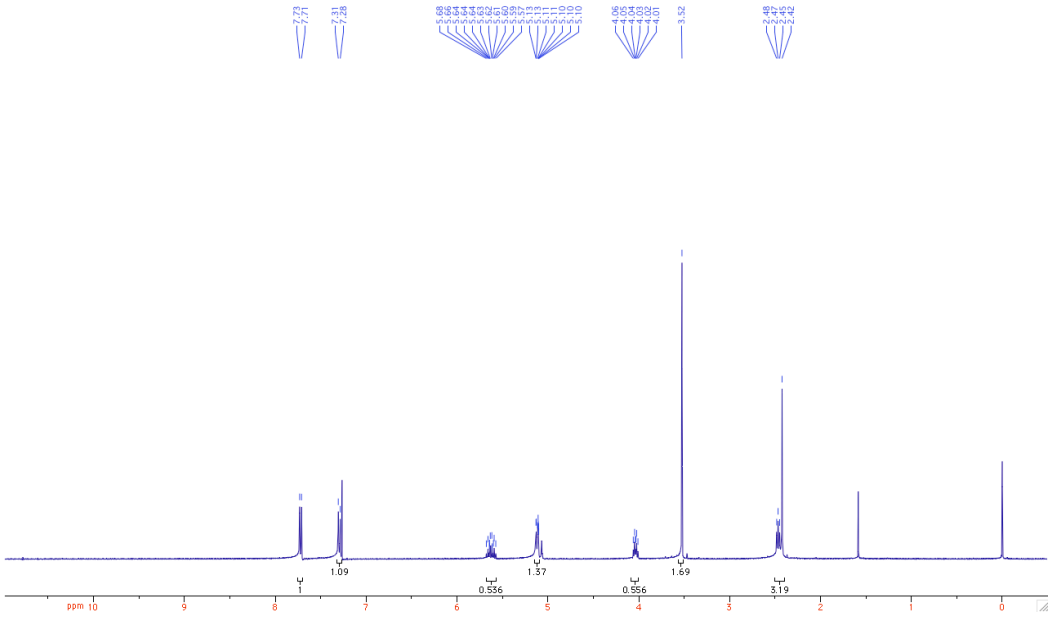


To a 0 ^{o}C mixture of aziridine (0.015 g, 0.05 mmol) in methylene chloride (0.5 mL) was added BF_3•Et_2O. The reaction was allowed to warm to room temperature and stirred for 5 hours. After quenching the reaction with Na_2CO_3 (sat) the product was extracted with methylene chloride. The combined organic fractions were dried over magnesium sulfate and the solvent was removed *in vacuo* giving a clear oil. No further purification was done: Exact mass calcd for $[C_{16}H_{23}NO_2SNa]$+ requires *m/z* 316.13 Found 316.13 (ESI+); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.72 (d, *J*=8 Hz, 2H), 7.27 (d, *J*=8 Hz, 2H), 3.64 (t, *J*=10 Hz, 1H), 3.02 (q, *J*=4 Hz, 1H), 2.58-2.65 (m, 1H), 2.42 (s, 3H), 2.14 (q, *J*=8 Hz, 1H), 1.83-1.91 (m, 2H), 1.68-1.75 (m, 2H), 1.58-1.65 (m, 2H), 1.41 (s, 6H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 120.5, 127.4, 58.6, 55.2, 39.0, 32.3, 28.7, 28.6, 26.5, 24.7, 21.9 ppm.

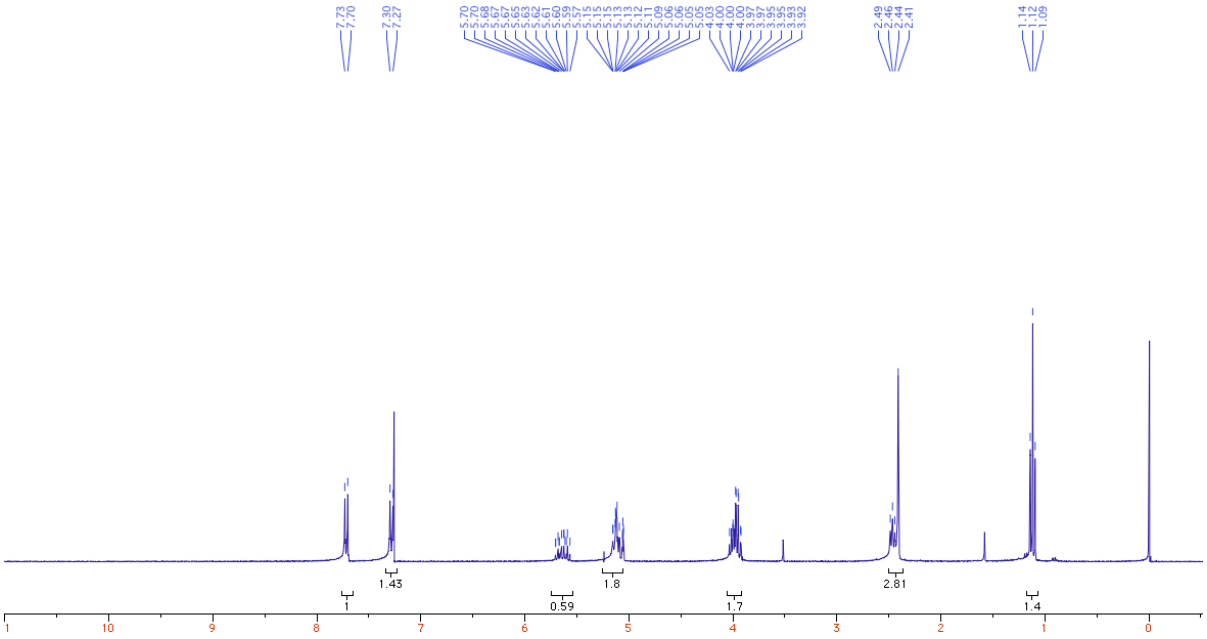
^{1}H NMR of Allyl glycine methyl ester



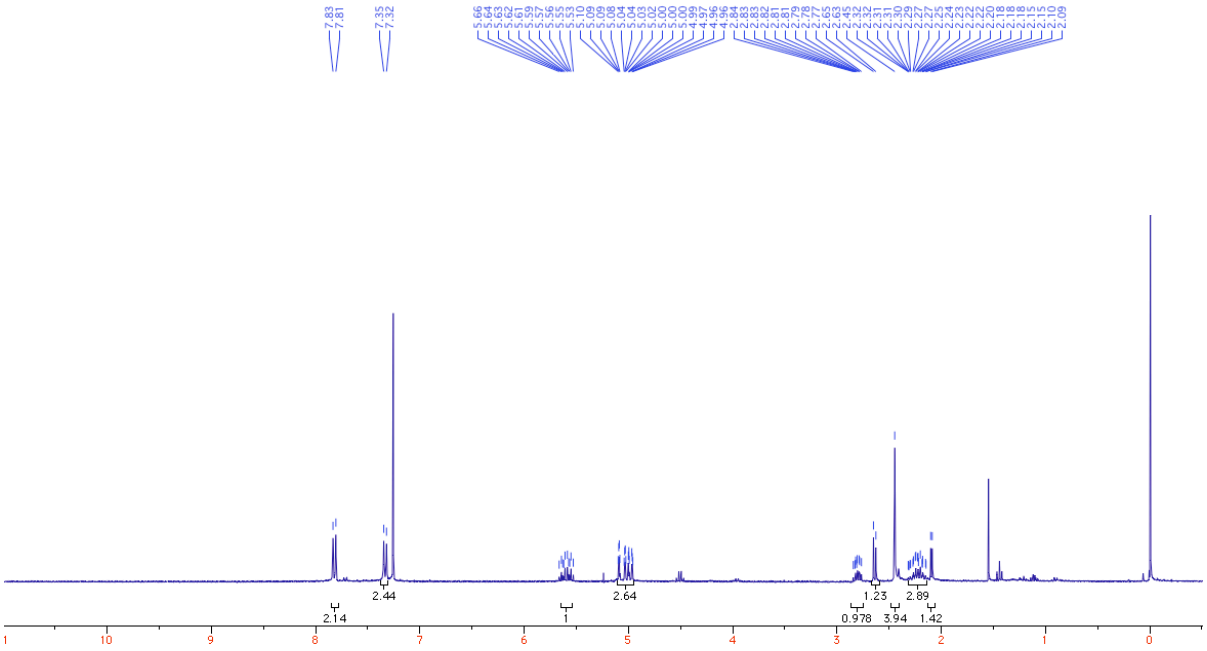
^{1}H NMR of Methyl 2-(4-methylphenylsulfonamido)pent-4-enoate (**51**)



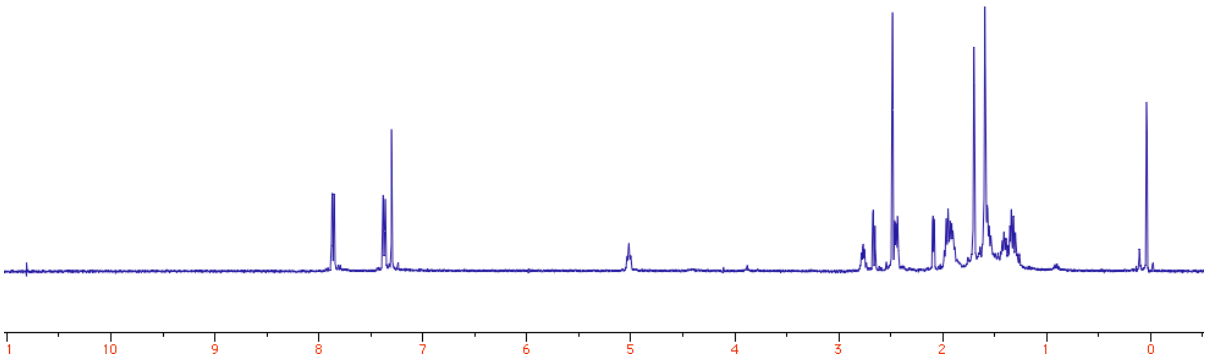
^{1}H NMR of *N*-(1-hydroxypent-4-en-2-yl)-4-methylbenzenesulfonamide (**52**)



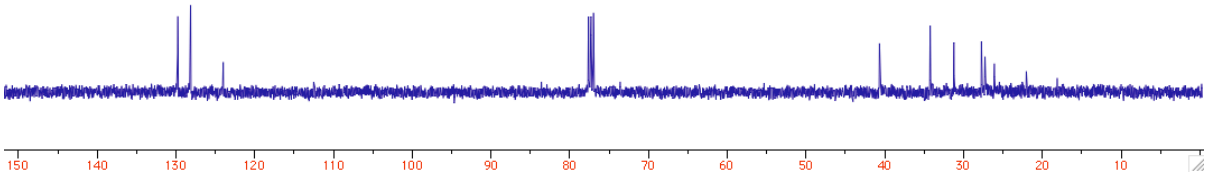
^{1}H NMR of 2-allyl-1-tosylaziridine (**53**)



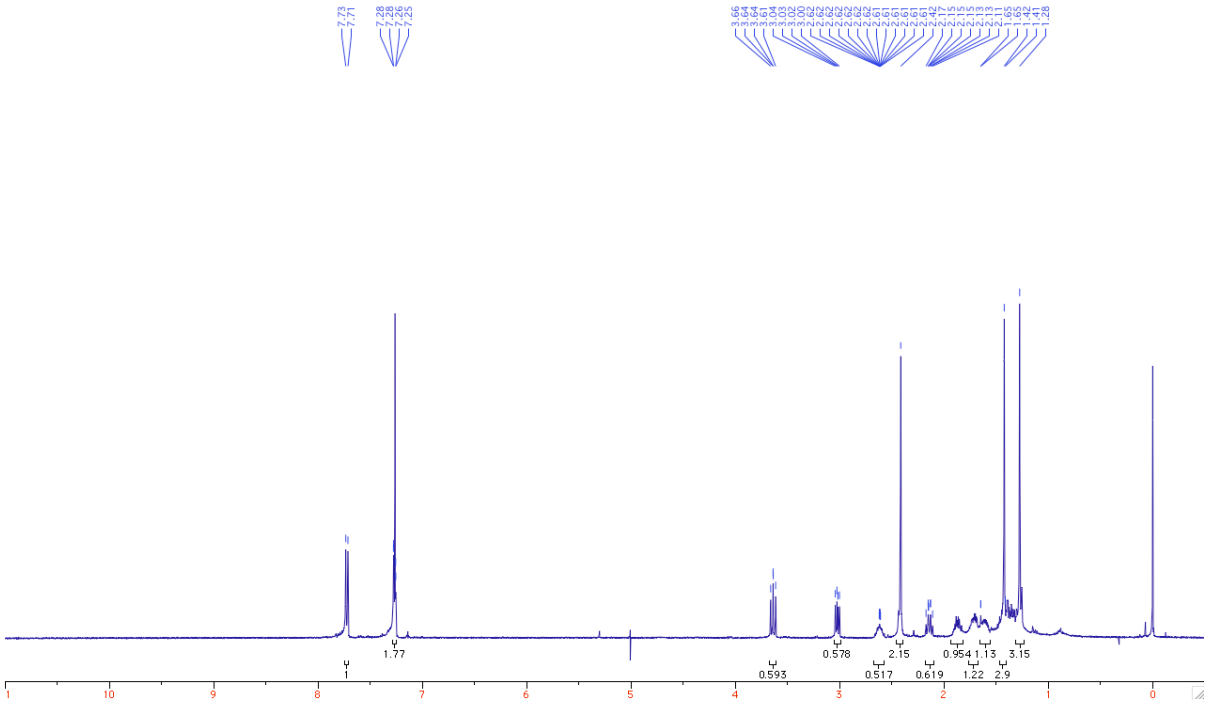
^{1}H NMR of 7-methyl oct-6-ene-1-tosylaziridine (**8**)



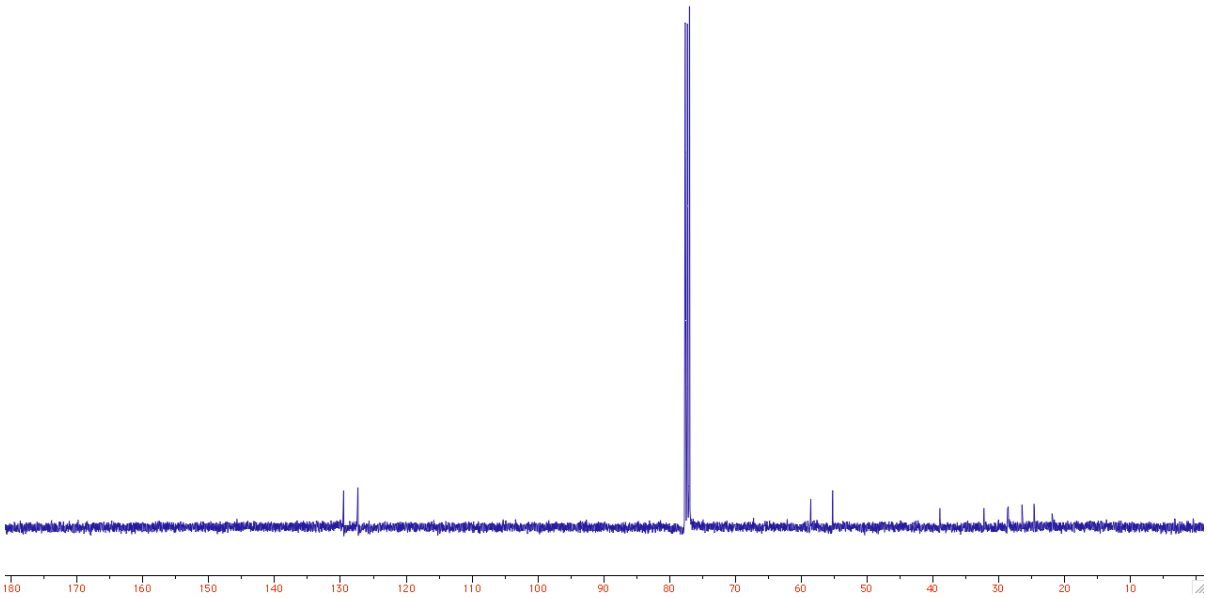
^{13}C NMR of 7-methyl oct-6-ene-1-tosylaziridine (**8**)



^{1}H NMR of 1,1-dimethyl-2-tosyloctahydrocyclopenta[c]pyrrole (**9**)

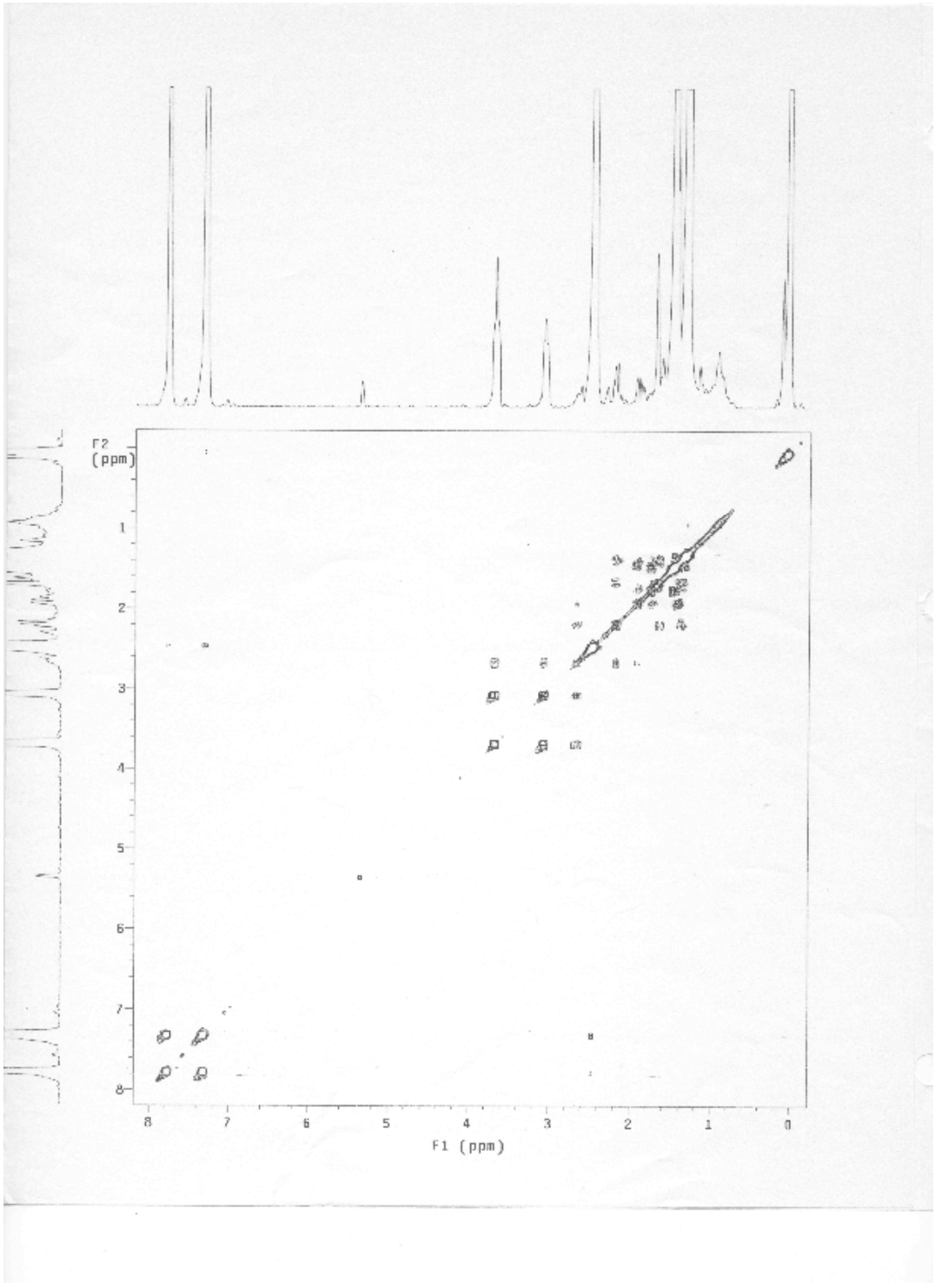


^{13}C NMR of 1,1-dimethyl-2-tosyloctahydrocyclopenta[c]pyrrole (**9**)



COSY NMR of 1,1-dimethyl-2-tosyloctahydrocyclopenta[c]pyrrole (**9**)

nt=16; ni=512; sfrq=400.022; solvent $CDCl_3$



Chapter 2: Kinetic Resolution of 4-hydroxymethyl cyclopent-2-enone

2.1 Kinetic Resolution as a Synthetic Tool

There are many benefits associated with kinetic resolutions, including ease of purification and the ability to isolate both enantiomers of a compound. For this reason resolutions are a versatile tool in organic synthesis. Despite the inherent drawback of a maximum yield of 50%, on the appropriate system this methodology can provide an excellent means for obtaining optically pure substrates. There have been significant efforts in making kinetic resolutions applicable for a variety of different reaction types, including reduction, oxidation, ring opening, and acylation reactions.[27] Complementing the expanding number of processes that can be used in performing kinetic resolutions is the effectiveness shown with a variety of different catalysts. Organic, organometallic, and enzymatic catalysts have all been utilized, with enzymatic methods generally providing the highest levels of selectivity. [28]

The Sharpless asymmetric epoxidation has been used to perform kinetic resolutions on various allylic alcohols. Utilizing a titanium-based catalyst, with *tert*-butyl hydroperoxide as the stoichiometric oxidant, the Sharpless epoxidation allows for access to either enantiomer of an allylic alcohol through the use of (+) or (-) tartrate esters as chiral ligands (Scheme 12).[29]

---

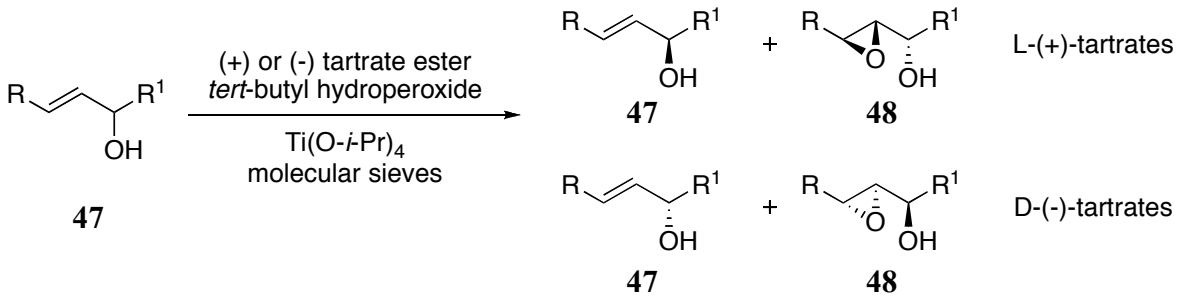
[27] (a) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 5-26. (b) Nicolaou, K. C.; Vourloumis, D.; Winssinger, N.; Baran, P. S. *Angew. Chem. Int. Ed.* **2000**, *39*, 44-122.

[28] (a) Wong, C.-H. *Science* **1989** *244*, 1145-1152. (b) Kazlauskas, R. J.; Weissfloch, A. N. E.; Rappaport, A. T.; Cuccia, L. A. *J. Org. Chem.* **1991**, *56*, 2656-2665. (c) Kim, M.-J.; Choi, Y. K. *J. Org. Chem.* **1992**, *57*, 1605-1607.

[29] (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5976-5978. (b) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237-6240. (C) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765-5780.

This procedure allows for the kinetic resolution of over 170 substrates with high levels of selectivity.

Scheme 12: Sharpless asymmetric epoxidation



2.2 Kinetic Resolutions of Primary Alcohols

Kinetic resolutions of primary alcohols provide an intriguing challenge in organic synthesis. Compared to secondary alcohols, primary alcohols exhibit higher reactivity coupled with a stereocenter further removed, which adds extra challenge to differentiating two enantiomers of a substrate. While progress has been made on the resolution of specific substrates, there is still considerable room for improvement.

The availability of enzymes that have been successfully employed to resolve primary alcohols is somewhat low, especially when compared those used to resolve secondary alcohols. Intense optimization of conditions through variation of the acylating agent, temperature, or the use of additives can be performed to improve the low selectivity observed with many lipases used in the kinetic resolution of primary alcohols.[30]

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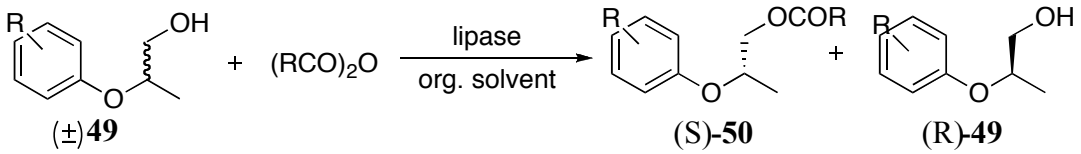
[30] (a) Weissfloch, A. N. E.; Kazlauskas, R. J. *J. Org. Chem.*, **1995,** *60*, 6959-6969. (b) Sakai, T.; Kishimoto, T.; Tanaka, Y.; Ema, T.; Utaka, M. *Tetrahedron Lett.* **1998**, 7881-7884. (c) Ema, T.; Maeno, S.; Takaya, Y.; Sakai, T.; Utaka, M. *J. Org. Chem.* **1996,** *61*, 8610-8616. (d) Ke, T.; Wescott, C. R.; Klibanov, A. M. *J. Am. Chem. Soc.* **1996**, *118*, 3366-3374. (e) Mezzetti, A.; Keith, C.; Kazlauskas, R. J. *Tetrahedron: Asymmetry*, **2003**, *14*, 3917-3924.

One example of an enzymatic resolution of primary alcohols is demonstrated in the work done by T. Miyazawa *et al*. with *Pseudomonas* sp. lipase to catalyze the acylation of 2-aryloxy-1-propanols **49**.[31] In this study, a number of anhydrides were explored for use as acyl donors, with hexanoic anhydride providing optimal selectivity for a variety of substrates (Scheme 13). As is often the case in asymmetric catalysis, lower temperature also contributed to the higher selectivity in this reaction.

Scheme 13: Enzymatic kinetic resolution of 2-aryloxy-1-propanols



(±)**49** (S)-**50** (R)-**49**

The effect of temperature on enzymatic resolutions of primary alcohols has also been reported by T. Sakai *et al*. in a study involving the lipase-catalyzed resolution of 5-(hydroxymethyl)-3-phenyl-2-isoxazoline (**51)**. This substrate has proven to be an important synthetic intermediate in the synthesis of β-hydroxy ketones, γ-amino alcohols, and β-amino acids.[32] In this work, it was reported that the kinetic resolution of **51** proceeded with poor selectivity at room temperature (E=5.9): however, performing the reaction at -60 ^{o}C increased the selectivity significantly (E=249) (Scheme 14).[33]

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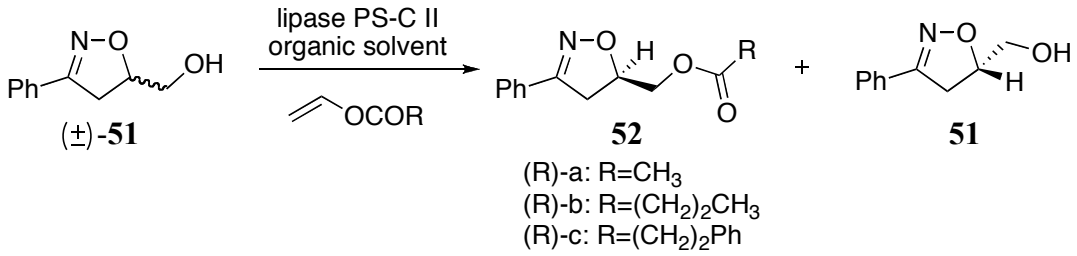
[31] Miyazawa, T.; Kaito, E.; Yukawa, T.; Murashima, T.; Yamada, T *Journal of Molecular Catalysis B: Enzymatic* **2005,** *37*, 63-67.

[32] Sakai, T.; Mitsutomi, H.; Korenaga, T.; Ema, T.; *Tetrahedron: Asymmetry* **2005**, *16*, 1535-1539.

[33] $E = K_{rel} = \dfrac{\ln[1 - c(1 + ee(p))]}{\ln[1 - c(1 - ee(P))]}$

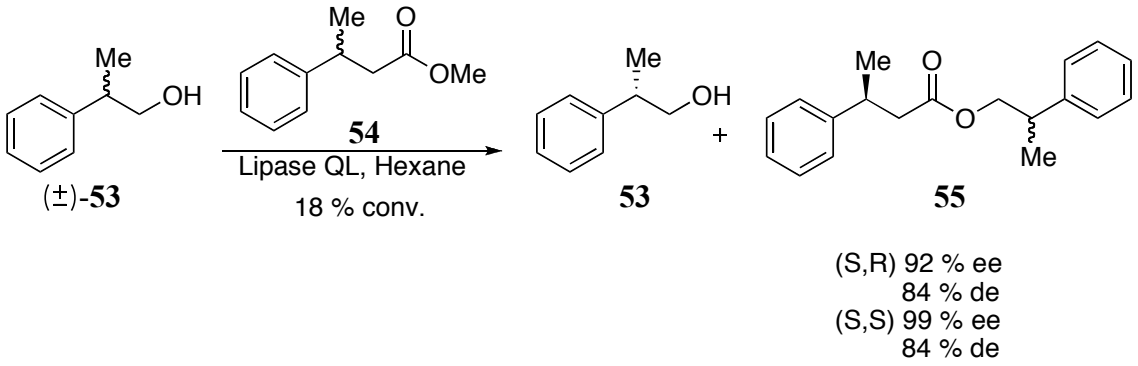
Chen, C.-S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294-7299.

Scheme 14: Kinetic resolution of 5-(hydroxymethyl)-3-phenyl-2-isoxazoline



Another method that has been utilized to improve the selectivity of a lipase catalyzed kinetic resolution is the use of chiral acyl donors. K. Hirose *et al.* reported enhanced selectivity (E=98) when using chiral acyl donor **54**, containing a stereocenter at the β-carbon to the carbonyl group, with the lipase SL in diisopropyl ether (Scheme 15).[34]

Scheme 15: Lipase catalyzed resolution of a primary alcohol using a chiral acylating agent

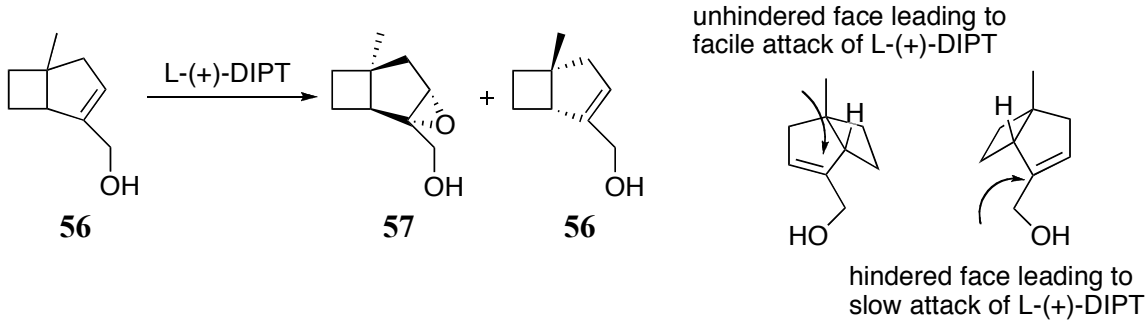


Although enzymes are commonly employed, they do not represent the sole method for kinetic resolutions of primary alcohols. Limited success in performing kinetic resolutions of primary alcohols using non-enzymatic methods has also been achieved. As with secondary alcohols, the Sharpless epoxidation provides an excellent method for performing kinetic resolutions on primary alcohols. Hamon and Tuck reported the use of the Sharpless

[34] Hirose, K.; Naka, H.; Yano, M.; Ohashi, S.; Naemura, K.; Tobe, Y. *Tetrahedron: Asymmetry* **2000**, *11*, 1199-1210.

epoxidation in the resolution of primary alcohol **56** in the synthesis of (+)-Grandisol (Scheme 16).[35]

Scheme 16: Asymmetric epoxidation in the resolution of a primary allylic alcohol



2.3 Desymmetrization of Glycerol Derivatives

Glycerol provides an interesting and useful substrate for the study and application of kinetic resolutions on primary alcohols. Glycerol is a triol that provides the backbone for many biological compounds such the phosphatidylinositol phosphate family of natural products.[36]

Examples for the preparation of optically active glycerol derivatives include recent work that has focused on kinetic resolutions involving both enzymatic and non-enzymatic catalysts. Recently, a method involving the use of small proline-based catalyst **59** was reported in the resolution of a protected glycerol derivative **58**. With this technique it was possible to achieve 97 % ee at 60 % conversion giving a 29 % yield of the desired enantiomer (Scheme 17).[37]

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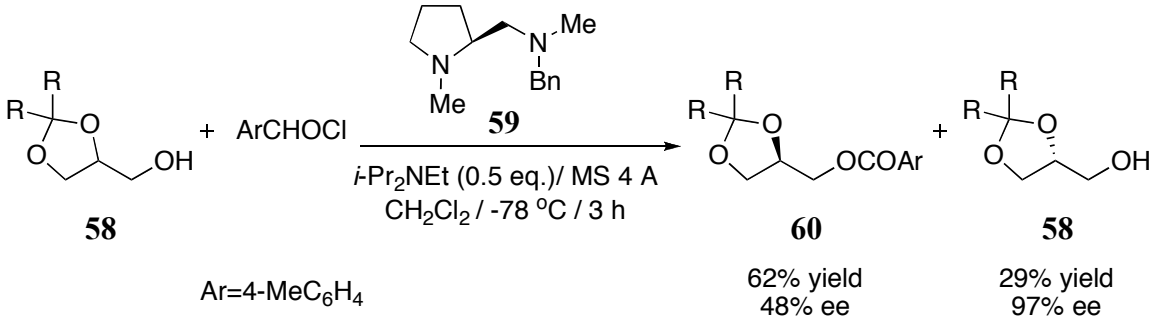
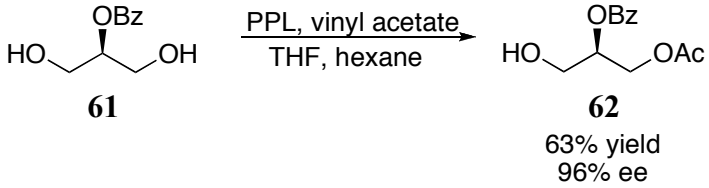
[35] Hamon, D. P. G.; Tuck, K. L. *J. Org. Chem.* **2000**, *65*, 7839-7846.
[36] (a) Martin, T. F. J. *Annu. Rev. Cell Developmental Biol.* **1998**, *14*, 231-264. (b) Czech, M. P. *Cell* **2000**, *100*, 603-606.
[37] Terakado, D.; Koutaka, H.; Oriyama, T. *Tetrahedron: Asymmetry* **2005**, *16*, 1157-1165.

Scheme 17: Kinetic resolution of glycerol with proline based catalyst



Similar to kinetic resolutions of other primary alcohols, lipases have shown promise in the desymmetrization of glycerol derivatives. In particular, the use of porcine pancreatic lipase (PPL) was shown to give selectivity (96 % ee with 63 % yield) in the desymmetrization of glycerol **61** (Scheme 18).[38]

Scheme 18: Enzymatic desymmetrization of glycerol

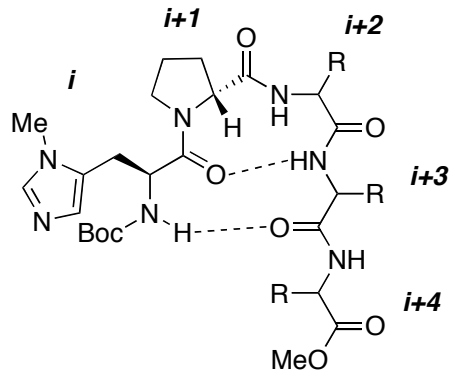


As an ongoing investigation of peptides as acyl transfer catalysts, the Miller lab has focused efforts on developing a catalyst for the desymmetrization of glycerol derivatives.[39] A solution to this challenge was the use of pentameric peptides containing the catalytic π-methyl-histidine residue.[40] Control of the peptides' secondary structures was achieved by

[38] Bodai, V.; Novak, L.; Poppe, L. *Synlett* **1999**, *6*, 759-761.
[39] The advantage of desymmetrization over kinetic resolutions is a theoretical 100% conversion with a >98 %ee leading to a more efficient process.
[40] (a) Miller, S. J.; Copeland, G. T.; Papaioannou, N.; Horstmann, T. E.; Ruel, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 1629-1630. (b) Jarvo, E. R.; Copeland, G. T.; Papaioannou, N.; Bonitatebus, P. J. Jr.; Miller, S. *J. Am. Chem. Soc.* **1999**, *121*, 11638-11643.

using D-proline at the *i+1* position, presumably forcing a β-hairpin in the peptide backbone (Figure 2).[41]

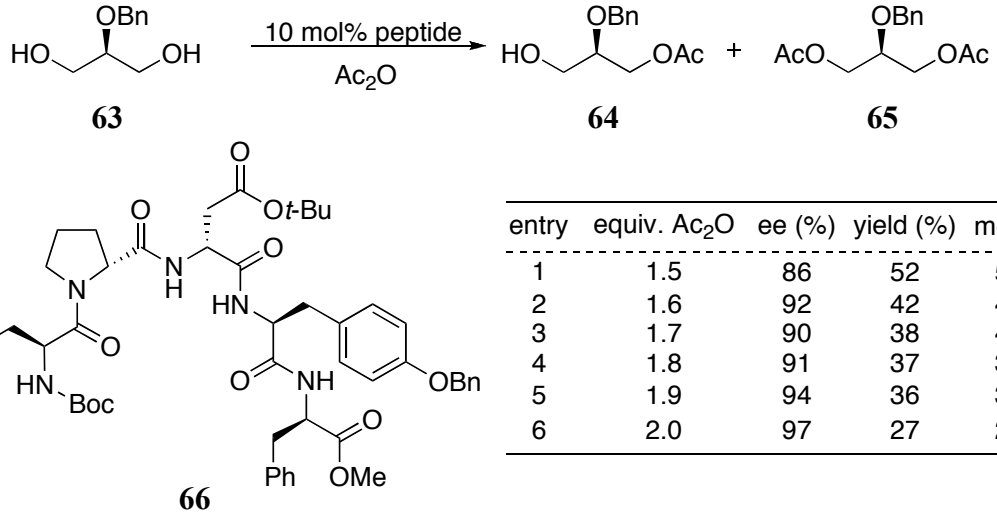
Figure 2: Pentameric peptides containing a β-turn



As expected, bridging from the kinetic resolution of secondary alcohols to primary alcohols required the optimization of reaction conditions, with temperature being a prevalent factor in controlling selectivity. Compared with secondary alcohols, where excellent selectivity was observed at room temperature, optimal conditions for glycerol involved lowering the temperature to -50 ^{o}C. [42] Further optimization of reaction conditions indicated that addition of extra acetic anhydride led to higher optical purity. Presumably this boost in enantiomeric purity results from a secondary kinetic resolution occurring under these reaction conditions (Scheme 19).[43]

[41] Blank, J. T.; Guerin, D. J. Miller, S. J. *Org. Lett.* **2000,** *2*, 1247-1249.
[42] Lewis, C. A.; Sculimbrene, B. R.; Xu, Y.; Miller S. J. *Org. Lett.* **2005**, *7*, 3021-3023.
[43] Schreiber, S. L.; Schreiber T. S.: Smith, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 1525-1529.

Scheme 19: Desymmetrization of glycerol



entry	equiv. Ac_2O	ee (%)	yield (%)	mono:bis
1	1.5	86	52	59:41
2	1.6	92	42	46:54
3	1.7	90	38	42:58
4	1.8	91	37	39:61
5	1.9	94	36	39:61
6	2.0	97	27	29:71

2.4 Use of 4-Hydroxymethyl Cyclopent-2-enone (76)

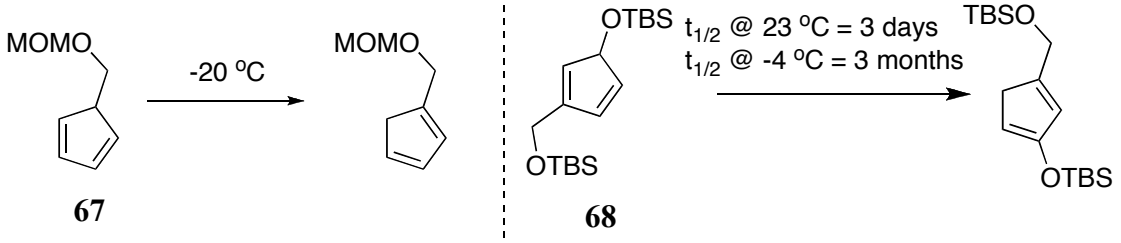
In an effort to further expand the utility of peptides as asymmetric catalysts the kinetic resolution of 4-hydroxymethyl cyclopent-2-enone (**76**) was investigated. This work was initiated through collaboration with the Gleason group from McGill University. 4-Hydroxymethyl cyclopent-2-enone (**76**) provides a synthetically useful intermediate that challenges the limitations of kinetic resolutions.

The Gleason group has discovered that 5-substitued cyclopentadienes **67** undergo 1,5-hydride-shifts at low temperature (-20 ^{o}C). By hydroxylating 5-substituted cyclopentadienes **67** at the 2-position the compound gains thermal stability (Scheme 20A). The Gleason group has shown that these compounds can undergo a variety of cycloaddition reactions. Utilizing this chemistry, efforts in that group are currently focused on the total synthesis of Palau'amine (**71**) and the core of the CP class of natural products, CP 225,917 (**74**) (Scheme 20).[44]

[44] Unpublished results from the Gleason group

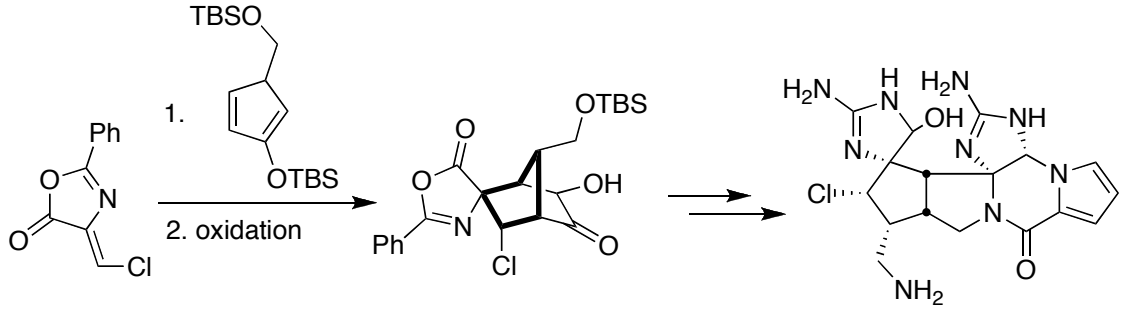
Scheme 20: Use of 4-hydroxymethyl-cyclopent-2-enone by the Gleason group

A: 1,5 hydride shift



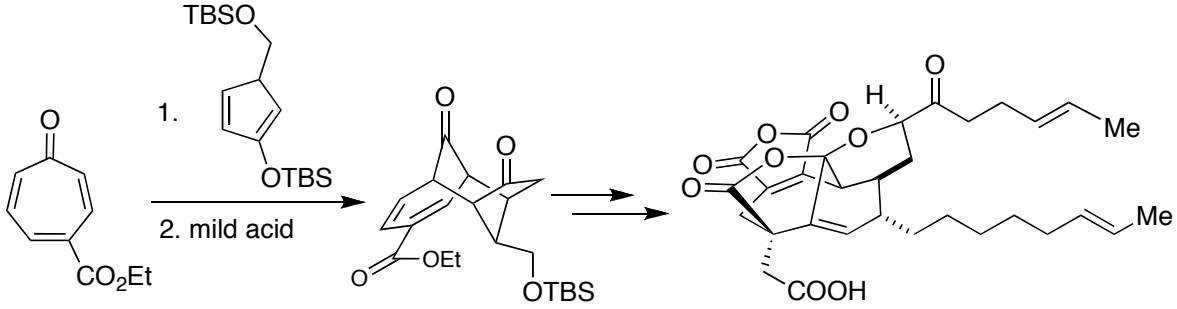
67 **68**

B: Synthesis of palau'amine



69 **70** palau'amine (**71**)

C: Synthesis of CP 225,917

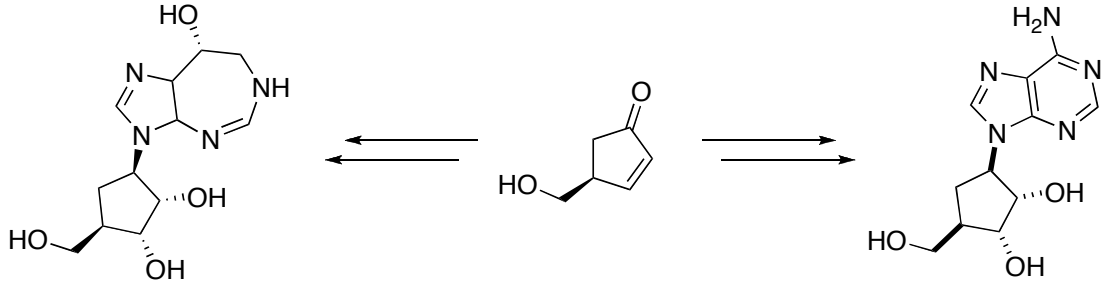


72 **73** CP 225,917 (**74**)

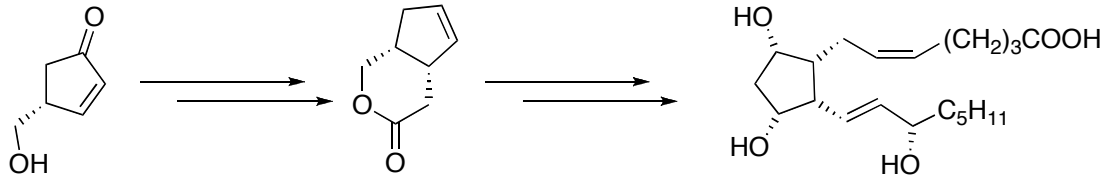
Along with providing a key intermediate for the synthesis of palau'amine and the CP class of natural products, 4-hydroxymethyl cyclopent-2-enone (**76**) provides a synthetic intermediate for other natural products as well. In particular, this intermediate was utilized in

the synthesis of aristeromycin (**77**)[45] and carbocyclic dideoxyhydronucleosides **75**,[46] along with the prostaglandin precursor 15-F_{2C}-IsoP (**79**) (Scheme 21).[47]

Scheme 21: Use of 4-hydroxymethylcyclopent-2-enone (**76**) in organic synthesis



carbocyclic coformycin (**75**) **76** (-)-aristeromycin (**77**)



76 **78** 15-F_{2c}-IsoP (**79**)

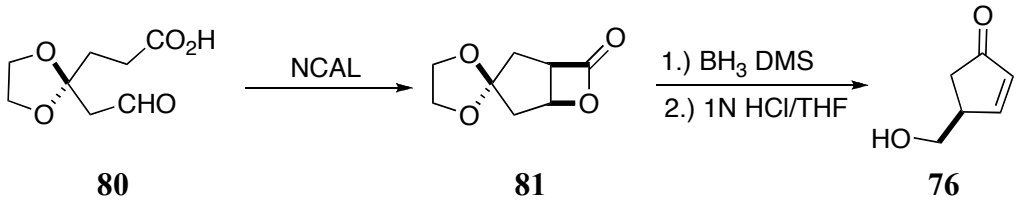
2.5 Preparation of 2-Hydroxymethyl Cyclopent-2-enone (76)

Previously reported methods for the synthesis of 2-hydroxymethyl cyclopent-2-enone (**76**) involve multiple steps with a low overall yield. Also problematic for these methods is the necessity to separate diastereomers to achieve optically active material. These problems make these methods unsuitable for large-scale production.[48] Cortez *et al.* reported one of the most

[45]Yokato, Y.; Cortez, G. S.; Romo, D. *Tetrahedron* **2002**, *58*, 7075-7080.
[46]Saville-Stones, E. A.; Turner, R. M.; Lindell, S. D.; Jennings, N. S.; Head, J. C.; Carver, D. S. *Tetrahedron* **1994**, *50*, 6695-6704.
[47]Zanoni, G.; Re, S.; Meriggi, A.; Castronovo, F.; Vidar, G. *Tetrahedron: Asymmetry* **2001**, *12*, 1785-1792.
[48] Yokato, Y.; Cortez, G. S.; Romo, D. *Tetrahedron* **2002**, *58*, 7075-7080.

efficient syntheses of this alcohol, involving a nucleophilic catalyzed aldol lactonization (NCAL) (Scheme 22).[49]

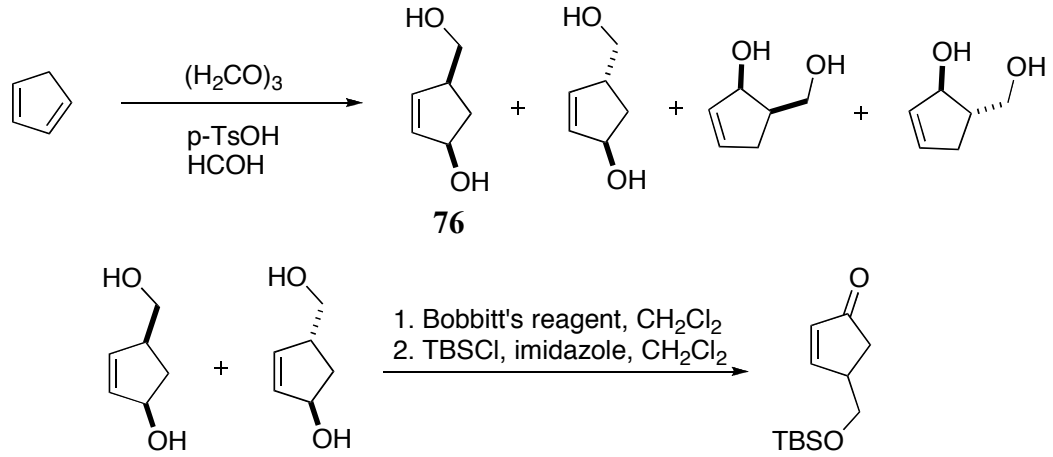
Scheme 22: Aldol lactonization



80 **81** **76**

In overcoming this problem, the Gleason group has developed a four step synthetic method for the preparation of racemic 2-hydroxymethyl cyclopent-2-enone (**76**).[50] The first step to this synthesis is a Prins reaction, in which cyclopentadiene is treated with paraformaldehyde, *p*-toluenesulfonic acid and formaldehyde. Unfortunately, this reaction results in a mixture of four distinct products, complicating the purification and making the protection of the alcohol necessary for isolation of the desired product. Further oxidation of the allylic alcohol selectively, using Bobbitt's reagent, gives the desired product (Scheme 23).

Scheme 23: Gleason group synthesis of 4-hydroxymethyl-cyclopent-2-enone (**76**)



76

[49] (a) Cortez, G. S.; Tennyson, R. L.; Romo, D. *J. Am. Chem. Soc.* **2001**, *123*, 7945-7946. (b) Yokota, Y.; Cortez, G. S.; Romo, D. *Tetrahedron* **2002**, *58*, 7075-7080.
[50] unpublished results from Gleason group

Despite the ability of 2-hydroxymethyl cyclopent-2-enone (**76**) to be synthesized on large scale there are limitations associated with the procedure developed by Gleason. The formation of multiple products and the lack of an enantioselective process hinder the effectiveness of this procedure in preparing intermediates in the synthesis of optically active natural products. To strengthen this methodology, the possibility of utilizing a peptide to perform a kinetic resolution of the product was investigated. Additionally, it was envisaged that this peptide or an alternative peptide might be able to perform a resolution of the different regioisomers produced in the Prins reaction. By utilizing a kinetic resolution in this procedure, isolation of both enantiomers of 2-hydroxymethyl cyclopent-2-enone (**76**) is possible.

2.6 Results and Discussion

Successful application of pentameric peptides in the desymmetrization of glycerol prompted the use of these catalysts for the initial investigation into the kinetic resolution of 2-hydroxymethyl cyclopent-2-enone (**76**). As in the glycerol project, attention was focused on β-turn peptides containing D-proline at the *i+1* position, with π-methylhistidine used as the catalytic moiety. The initial screen revealed interesting results, with one peptide (Table 2, entry 1) showing moderate selectivity (k_{rel}=1.2). For the initial screen the reaction was run at -30 ^{o}C with one equivalent of Hünig's base and 5 mol % peptide in chloroform (Scheme 24).[51,52]

[51] In the initial screen ee was determined by Chiral HPLC and conversion by ^{1}H NMR
[52] Initial Screen preformed with help from Chad Lewis

Scheme 24: Kinetic resolution of 4-hydroxymethyl cyclopent-2-enone (**76**)

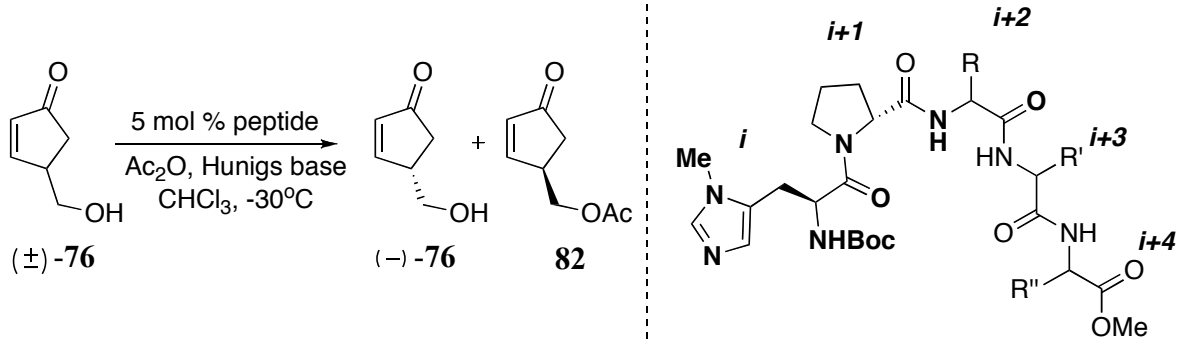


Table 2: Initial screen of 4-hydroxymethyl cyclopent-2-enone

	i+1	***i+2***	***i+3***	***i+4***			
entry		Peptide				conv.*	ee(Prod)**
1	PMH	D-Pro	Dbg	Phe	D-Phe	79%	-19%
2	PMH	D-Pro	Abu	Phe	D-Phe	63%	-13%
3	PMH	D-Pro	Chg	Phe	D-Phe	78%	-13%
4	PMH	D-Pro	Ile	Phe	D-Phe	80%	-13%
5	PMH	D-Pro	Leu	Phe	D-Phe	86%	-13%
6	PMH	D-Pro	D-HPhe	Phe	D-Phe	80%	10%
7	PMH	D-Pro	Asp(Obut)	Phe	D-Phe	78%	-11%
8	PMH	D-Pro	HPhe	Phe	D-Phe	73%	-11%
9	PMH	D-Pro	Sp8	Phe	D-Phe	72%	-10%
10	PMH	D-Pro	Phg	Phe	D-Phe	82%	-10%
11	PMH	D-Pro	Sp6	Phe	D-Phe	63%	-8%
12	PMH	D-Pro	Asn(Trt)	Phe	D-Phe	80%	-8%
13	PMH	D-Pro	D-Val	Phe	D-Phe	63%	6%
14	PMH	D-Pro	His(Bzl)	Phe	D-Phe	70%	-3%

* Conversion determined by NMR
** ee Determined by Chiral HPLC

Further reaction optimization demonstrated that lower temperatures contribute significantly to the selectivity observed. By lowering the reaction temperature to -50 ^{o}C, reactivity was conserved while the selectivity increased from a k_{rel}=1.3 to a k_{rel}=3.5 for the lead peptide (Table 2, entry 2). From this preliminary optimization two lead peptides (Table 2, entries 1 and 2) provided moderate selectivity (k_{rel}'s=3.7 and 3.5 respectively). These peptides were the basis on which further catalyst optimization was built.

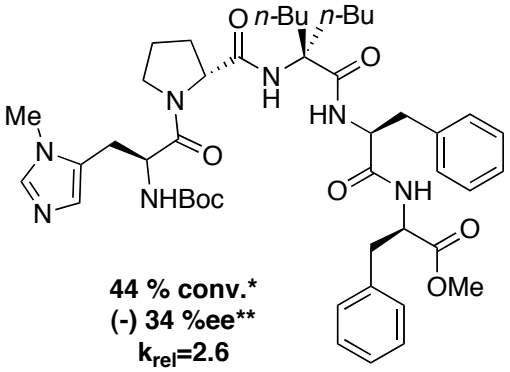
Table 3: Temperature effects on the kinetic resolution of 4-hydroxymethyl cycloopent-2-enone

	i+1	*i+2*	*i+3*	*i+4*	-30 °C		-50 °C	
entry		Peptide			conv.*	ee(Prod)**	conv.*	ee(Prod)**
1	PMH	D-Pro	Aib	D-Trp(Boc)	D-Phe	--	--	50%	43%
2	PMH	D-Pro	Dbg	Phe	D-Phe	79%	-19%	44%	-34%
3	PMH	D-Pro	Chg	Phe	D-Phe	78%	-13%	51%	-23%
4	PMH	D-Pro	Leu	Phe	D-Phe	86%	-13%	52%	-23%
5	PMH	D-Pro	Ile	Phe	D-Phe	80%	-13%	56%	-20%
6	PMH	D-Pro	Abu	Phe	D-Phe	63%	-13%	42%	-17%
7	PMH	D-Pro	D-HPhe	Phe	D-Phe	80%	10%	49%	17%
8	PMH	D-Pro	D-Asp(O*t*-Bu)	Tyr(Bn)	D-Phe	--	--	43%	-9%

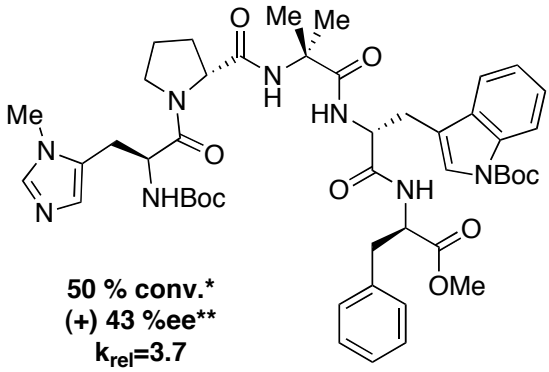
* Conversion determined by NMR
** ee Determined by Chiral HPLC

Upon further examination of these two catalysts (table 2, entries 1 and 2) the difference in selectivity observed of interest due to the similarities in structure of both peptides (Figure 3). Entry 1 has a Boc protected D-tryptophan [D-trp(Boc)] at the *i+3* position and entry 2 contains an L-phenylalanine (Phe) at that same position. Both peptides contain a geminally substituted aliphatic amino acid at *i+2* and D-phenylalanine at the terminal *i+4* position. Of particular interest in this data is that while the same antipode of π-methylhistidine is used in all these peptides, selectivity of the two lead catalysts is for different enantiomers of the substrate.

Figure 3: Lead catalyst after preliminary screen



44 % conv.*
(-) 34 %ee**
k_{rel}=2.6



50 % conv.*
(+) 43 %ee**
k_{rel}=3.7

The analytical technique utilized for determination of enantioselectivity and conversion also required optimization. Initial analysis for the peptide screens were

preformed utilizing chiral HPLC for selectivity, and ^{1}H NMR for conversion. This method required a 60 min HPLC method and provided no separation for the starting material: only for the acylated product. Because of the volatility associated with both the product and starting material it was decided to utilize chiral GC for the determination of both conversion and selectivity. This method allowed for the separation of both product and starting material enantiomers in less time, making a higher throughput screening technique practical.

A number of peptide libraries were prepared and studied in an effort to establish further understanding of this system. Using a systematic approach for catalyst optimization, each position of the peptides was altered individually while conserving the rest of the catalyst. Various amino acids were used to investigate effects of stereochemistry, size and electronics at individual locations within the peptide (Table 4).[53]

Table 4: Top catalyst for the kinetic resolution of 4-hydroxy cyclopent-2-enone

		i+1	*i+2*	*i+3*	*i+4*					
entry			Peptide			conv.*	ee(SM)*	ee(Prod)*	k_{rel}(SM)**	k_{rel}(prod)**
1	PMH	D-Pro	Aib	D-Cha	Gly	55%	-49%	57%	3.9	6.9
2	PMH	D-Pro	Aib	D-1-Nal	Gly	40%	-24%	53%	2.7	4.5
3	PMH	D-Pro	Aib	D-Lys(Boc)	Gly	36%	-22%	51%	2.8	4.0
4	PMH	D-Pro	Aib	D-Trp(Boc)	Ala	59%	-52%	47%	3.5	5.3
5	PMH	D-Pro	Aib	D-Trp(Boc)	Trp(Boc)	56%	-44%	46%	3.1	4.8
6	PMH	D-Pro	Aib	D-Trp(Boc)	Gly	72%	-66%	43%	5.0	4.6
7	PMH	D-Pro	D-Val	D-Trp(Boc)	Gly	30%	-20%	57%	3.3	4.8

* Conversion ane ee's determined by Chiral GC

** k_{rel}'s calculated according to the method of Kagan:
(Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1998**, 18, 249-330)

The peptides giving the highest selectivity exhibit some common structural features. Of particular notice is the importance of stereochemistry at the *i+3* position. Both D- and L- amino acids were incorporated at this position with a noticeable enhancement in selectivity observed with D-amino acids. Apart from the stereochemistry at the *i+3*

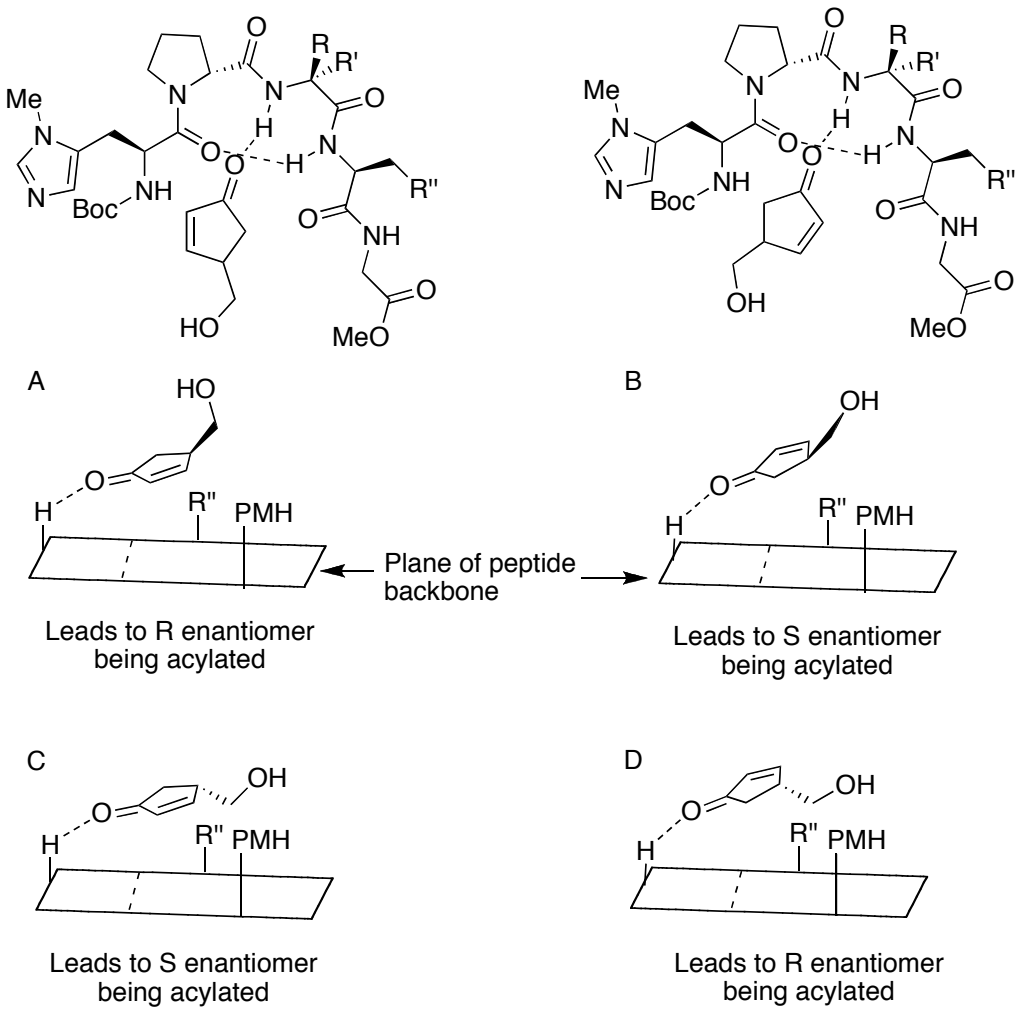
[53] For a complete list of peptides screened see the appendix, Page 48

position, the choice of amino acid side chain also plays an important role. Of all the amino acids screened at this position, the highest selectivity was seen with D-cyclohexylalanine (D-Cha), (1-naphthyl)-D-alanine (D-1-Nal) and D-tryptophan [D-trp(Boc)].

To further understand the selectivity of this system, a model was constructed in an effort to predict the binding between the substrate and catalyst (Figure 4). Assuming the β-turn confirmation of the peptide remains in place during this reaction, the selectivity observed can be traced to the substrate orientation. Further hypothesizing that the substrate catalyst binding is a result of a hydrogen bond between the amide of the *i+2* amino acid and the enone of the substrate, there are four possible ways in which the substrate can align itself with the peptide (Figure 4 A-D).

Drawing on the fact that the R enantiomer is being acylated at a higher rate than the S enantiomer, the binding of the substrate with the catalyst is further reduced to two possibilities (Figure 4, A and D). From preliminary data, both of these possibilities can be used to justify the outcome observed for the top peptides. Selectivity in this system would result from either a positive electronic interaction with the enone and a π-system at the *i+3* position, (1-naphthyl)-D-alanine (D-1-Nal) and D-tryptophan [D-trp(Boc)]. Alternatively, a negative steric interaction between the sp^3 carbon of cyclopentane and the amino acid at the *i+3* position causes this orientation to be disfavored, D-cyclohexylalanine (D-Cha).

Figure 4: Potential binding of substrate to peptide



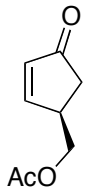
2.7 Conclusion

Future experiments would help to demonstrate the accuracy of this model. Initial experiments that could be performed would be to insert a stronger hydrogen bond donating amino acid residue in the *i+2* position, leading to stronger binding of the catalyst with the substrate. Along these same lines, it would be interesting to replace the amide bond believed to be involved in binding with an alkene isostere to observe the selectivity when that

hydrogen bond donor is removed. Another interesting experiment to perform would be a truncation of the peptide to explore the selectivity seen when different residues are removed.

2.8 Experimental

General procedure for the kinetic resolution of 4-hydroxymethylcyclopent-2-enone (**76**)



The alcohol was dissolved in $CHCl_3$ and cooled to -50 ^oC. To this solution was added Et_3N and the catalyst (50 μM in CH_2Cl_2). The reaction was stirred at -50 ^oC for 20 min at which time the acetic anhydride was added. The reaction stirred at -50 ^oC for 12 hours and was quenched with MeOH. Purification of the individual reactions was done by running the crude material through a short plug of silica gel eluting with Et_2O. Removal of the solvent in vacuo gave a clear oil. Analysis of this reaction via chiral gas chromatography: Chiral BDM column, 30 meters, 0.25 mm diameter, flow rate at 150 ^oC, 15 min. retention times product 8.841 min (R) enantiomer 9.246 min (S) enantiomer Starting material 11.725 min (S) enantiomer 12.597 min (R) enantiomer.

Absolute stereochemistry was determined by the optical rotation of the isolated starting material from the kinetic resolution, purified by flash column chromatograph and eluting with 100 % ether.

$[\alpha]_D^{25}$ =-27. (c= 1, CH_2Cl_2) for -66% ee: Giving the (S) enantiomer.

Literature value (R) enantiomer: $[\alpha]_D^{25}$ =+159 (c 0.5, CH_2Cl_2)[54]

General Procedure for Preparation of Peptide Using Solid Phase Synthesis

Peptides were synthesized on solid support using commercially available Wang polystyrene resin preloaded with the desired FMOC protected termial amino acid. Couplings were performed using 5 equiv amino acid derivative, 5 equiv HBTU, and 10 equiv Hunig's

[54] (a) Cortez, G. S.; Tennyson, R. L.; Romo, D. *J. Am. Chem. Soc.* **2001**, *123*, 7945-7946. (b) Yokota, Y.; Cortez, G. S.; Romo, D. *Tetrahedron* **2002**, *58*, 7075-7080.

base in DMF, for 3 h. Deprotections were performed using 20% piperdine in DMF for 20 min (to minimize diketopiperazine formation; dipeptides were deprotected using 50% piperdine in DMF for 5 min). Peptides were cleaved from solid support using a mixture of MeOH:DMF:NEt_3 (9:1:1) for 5 d. The peptides were used in parallel reaction screens without further purification.

Amino acid abbreviations

Aib: Aminoisobutyric Acid	1-Nal: 1-Napthylalanine
Ala: Alanine	Phe: Phenylalanine
Arg: Arginine	Phg: Phenylglycine
Cha: Cyclohexylalanine	Pip: Pipecolic acid
Chg: Cyclohexylglycine	Pro: Proline
Deg: Diethylglycine	PMH: π-methyl Histidine
Gly: Glycine	Ser: Serine
His: Histidine	Thr: Threonine
Ile: Isoleucine	Trp: Tryptophan
Leu: Leucine	Tyr: Tyrosine
Lys: Lysine	Val: Valine
Met: Methionine	

Peptides Screened in the Kinetic Resolution of 4-Hydroxymethyl cyclopent-2-enone (76)

Entry	Peptide	ee sm	ee prod	Conv.
1	PMH-ProD-ValD-TrpD(Boc)-Leu	-24.7	56.7	46
2	PMH-ProD-ValD-TrpD(Boc)-Gly	-19.9	58.1	30
3	PMH-ProD-Aib-1-NalD-Gly	-23.8	52.7	40
4	PMH-ProD-LysD(Boc)-TrpD(Boc)-Gly	-14.4	56.6	21
5	PMH-ProD-ArgD(Mtr)-TrpD(Boc)-Gly	-17.1	51.1	33
6	PMH-ProD-ChgD-TrpD(Boc)-Gly	-14.8	54.0	24
7	PMH-ProD-ChaD-TrpD(Boc)-Gly	-10.5	49.8	15
8	PMH-ProD-Cha-TrpD(Boc)-Gly	-5.7	31.6	18
9	PMH-ProD-Val-TrpD(Boc)-PheD	1.8	-1.5	57
10	PMH-ProD-ValD-TrpD(Boc)-PheD	-43	32	60
11	PMH-ProD-Chg-TrpD(Boc)-PheD	3.2	-4.7	66
12	PMH-ProD-Leu-TrpD(Boc)-PheD	-11	18	35
13	PMH-ProD-Phe-TrpD(Boc)-PheD	-6.8	11	39
14	PMH-ProD-Ser(Bn)-TrpD(Boc)-PheD	<5	<5	39
15	PMH-ProD-Lys(Boc)-TrpD(Boc)-PheD	-6.4	9.8	37
16	PMH-ProD-Ile-TrpD(Boc)-PheD	<5	<5	47
17	PMH-ProD-Met-TrpD(Boc)-PheD	-8.3	13	38
18	PMH-ProD-ProD-TrpD(Boc)-PheD	<5	<5	44
19	PMH-ProD-PheD-TrpD(Boc)-PheD	<5	<5	38
20	PMH-ProD-His(Trt)-TrpD(Boc)-PheD	<5	<5	40
21	PMH-ProD-Trp(Boc)-TrpD(Boc)-PheD	-9.7	15	41
22	PMH-ProD-Phg-TrpD(Boc)-PheD	-9.9	9.5	44
23	PMH-ProD-Deg-TrpD(Boc)-PheD	-23	25	51
24	PMH-ProD-Phe-Phe-PheD	-21	10	38
25	PMH-ProD-Deg-Phe-PheD	9.1	-12.4	49
26	PMH-ProD-His(Trt)-PheD	5.6	-5.7	61
27	PMH-ProD-Trp(Boc)-Phe-PheD	9.6	-15	43
28	PMH-ProD-Deg-Phe-Val	-5	<5	46
29	PMH-ProD-Deg-Phe-Ala	<5	-6	41
30	PMH-ProD-Deg-Phe-Trp(Boc)	<5	<5	41
31	PMH-ProD-Deg-Phe-Gly	<5	<5	54
32	PMH-ProD-Aib-Ala-PheD	-3.7	5.3	47
33	PMH-ProD-Aib-AlaD-PheD	-31.7	31.8	51
34	PMH-ProD-Aib-Gly-PheD	-9.9	9.8	53
35	PMH-ProD-Aib-Thr(Bn)-PheD	-9.8	11.2	50
36	PMH-ProD-Aib-Thr(tBu)-PheD	-14.1	13.8	50
37	PMH-ProD-Aib-Tyr(tBu)-PheD	6.5	-6.4	52
38	PMH-ProD-Aib-Arg(Pbf)-PheD	5.7	-7.4	59
39	PMH-ProD-Aib-TrpD(Boc)-Val	-25	32	44
40	PMH-ProD-Aib-TrpD(Boc)-Ala	-52	47	59
41	PMH-ProD-Aib-TrpD(Boc)-Trp(Boc)	-44	46	56
42	PMH-ProD-Aib-TrpD(Boc)-Gly	-66	43	72
43	PMH-ProD-Aib-TrpD(Boc)-Phe-PheD	-58	30	68

Entry	Peptide	ee sm	ee prod	Conv.
44	PMH-ProD-Aib-TrpD(Boc)-Trp(Boc)-PheD	-33	18	63
45	PMH-ProD-Aib-Phe-Phe-PheD	<5	-19	74
46	PMH-ProD-Aib-Phe-Trp(Boc)-PheD	<5	<5	65
47	PMH-ProD-Aib-Aib-Trp(Boc)-PheD	-12	12	49
48	PMH-ProD-Aib-TrpD(Boc)-Leu-PheD	-38	34	46
49	PMH-ProD-Chg-Phe-Aib-PheD	<5	-17	25
50	PMH-ProD-Chg-TrpD(Boc)-Gly-PheD	<5	<5	19
51	PMH-ProD-Aib-TrpD(Boc)-Gly-Ala	-13.5	39.8	28
52	PMH-ProD-Aib-TrpD(Boc)-Gly-Ala	-14.4	46.0	23
53	PMH-ProD-Aib-TrpD(Boc)-Gly-AlaD	-10.5	42.6	21
54	PMH-ProD-Aib-TrpD(Boc)-Gly-Bala	-16.5	39.1	36
55	PMH-ProD-Aib-TrpD(Boc)-Gly-Gly	-27.4	50.1	38
56	PMH-ProD-Aib-TrpD(Boc)-Gly-Val	-6.6	41.8	12
57	PMH-ProD-Aib-TrpD(Boc)-Gly-Trp(Boc)	-13.4	53.8	19
58	PMH-ProD-Aib-TrpD(Boc)-Gly-Aib	-2.5	36.7	11
59	PMH-ProD-Aib-TrpD(Boc)-Ala-PheD	-17.6	39.0	40
60	PMH-ProD-Aib-TrpD(Boc)-Ala-Ala	-17.7	38.0	31
61	PMH-ProD-Aib-TrpD(Boc)-Ala-AlaD	-8.9	32.0	25
62	PMH-ProD-Aib-TrpD(Boc)-Ala-Bala	-15.8	31.2	40
63	PMH-ProD-Aib-TrpD(Boc)-Ala-Gly	-21.1	31.0	49
64	PMH-ProD-Aib-TrpD(Boc)-Ala-Val	-5.8	20.3	16
65	PMH-ProD-Aib-TrpD(Boc)-Ala-Trp(Boc)	-15.3	34.0	29
66	PMH-ProD-Aib-TrpD(Boc)-Ala-Aib	0.0	15.5	1
67	PMH-ProD-Aib-TrpD(Boc)-AlaD-PheD	-19.4	38.5	34
68	PMH-ProD-Aib-TrpD(Boc)-AlaD-Ala	-10.5	34.9	23
69	PMH-ProD-Aib-TrpD(Boc)-AlaD-AlaD	-17.3	25.2	41
70	PMH-ProD-Aib-TrpD(Boc)-AlaD-B-ala	-20.8	41.0	34
71	PMH-ProD-Aib-TrpD(Boc)-AlaD-Gly	-18.1	46.8	28
72	PMH-ProD-Aib-TrpD(Boc)-AlaD-Val	-6.5	28.5	15
73	PMH-ProD-Aib-TrpD(Boc)-AlaD-Trp(Boc)	-11.4	37.4	23
74	PMH-ProD-Aib-TrpD(Boc)-AlaD-Aib	-1.0	13.4	13
75	PMH-ProD-Aib-TrpD(Boc)-TrpD(Boc)-PheD	-34.1	45.4	47
76	PMH-ProD-Aib-TrpD(Boc)-TrpD(Boc)-Ala	-20.5	51.1	33
77	PMH-ProD-Aib-TrpD(Boc)-TrpD(Boc)-AlaD	-17.9	49.3	30
78	PMH-ProD-Aib-TrpD(Boc)-TrpD(Boc)-Bala	-29.1	45.2	42
79	PMH-ProD-Aib-TrpD(Boc)-TrpD(Boc)-Gly	-40.6	48.5	53
80	PMH-ProD-Aib-TrpD(Boc)-TrpD(Boc)-Val	-4.7	27.2	11
81	PMH-ProD-Aib-TrpD(Boc)-TrpD(Boc)-Trp(Boc)	-0.5	0.3	11
82	PMH-ProD-Aib-TrpD(Boc)-TrpD(Boc)-Aib	-2.8	11.8	24
83	PMH-ProD-Aib-TrpD(Boc)-Trp(Boc)-PheD	-28.0	27.2	57
84	PMH-ProD-Aib-TrpD(Boc)-Trp(Boc)-Ala	-31.9	41.1	46
85	PMH-ProD-Aib-TrpD(Boc)-Trp(Boc)-AlaD	-16.6	27.8	35
86	PMH-ProD-Aib-TrpD(Boc)-Trp(Boc)-Bala	-9.3	22.1	29
87	PMH-ProD-Aib-TrpD(Boc)-Trp(Boc)-Gly	-27.4	27.8	54
88	PMH-ProD-Aib-TrpD(Boc)-Trp(Boc)-Val	-3.3	14.7	16

Entry	Peptide	ee sm	ee prod	Conv.
89	PMH-ProD-Aib-TrpD(Boc)-Trp(Boc)-Trp(Boc)	-12.4	26.4	34
90	PMH-ProD-Aib-TrpD(Boc)-Trp(Boc)-Aib	-1.3	18.1	0

Gas Chromatography Calibration for 4-Hydroxymethyl cyclopent-2-enone (76)

Standard solutions of 4-hydroxymethyl cyclopent-2-enone **82** and the OAc product were prepared (0.017 M in ethyl ether). These solutions were then combined in known amounts and run with the GC conditions previously reported. Data for this calibration is recorded in the table below.

Entry	Volume OH (uL)	Volume OAc (uL)	Total volume (uL)	Area OH	Area OAc
1	300	0	300	524	0
2	270	30	300	475	53
3	240	60	300	411	135
4	210	90	300	345	210
5	180	120	300	295	268
6	150	150	300	241	352
7	120	180	300	194	401
8	90	210	300	128	446
9	60	240	300	76	536
10	30	270	300	54	615
11	0	300	300	0	717

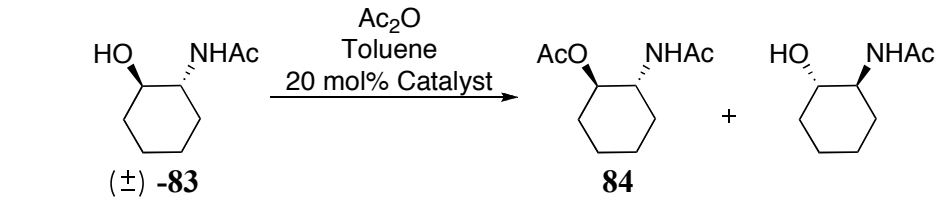
Chapter 3: Kinetic Resolution of Aliphatic Alcohols

3.1 Hydrogen Bonding in Peptide Catalysts

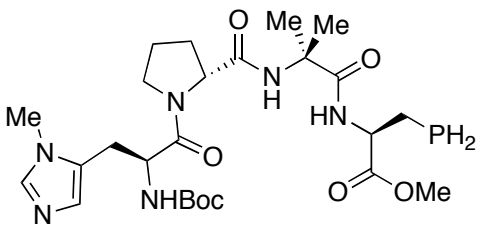
Central to the selectivity of peptide catalysts developed by the Miller group is the idea of positive non-covalent interactions between the substrate and catalyst. Presumably the most prevalent interaction exploited is a hydrogen bond between the amide of the peptide backbone (acting as a hydrogen bond donor) and a hydrogen bond acceptor of the substrate. In demonstrating the importance of this hydrogen bond interaction, studies were preformed incorporating alkene isosteres in place of the amide bonds of certain peptides. The initial hypothesis revolved around a key interaction between the acetamide of the substrate and the amide bond of the amino acid located at the apex of the β-turn (Scheme 25).[55]

[55] Miller, S. J. *Acc. Chem. Res.* **2004**, *37*, 601-610.

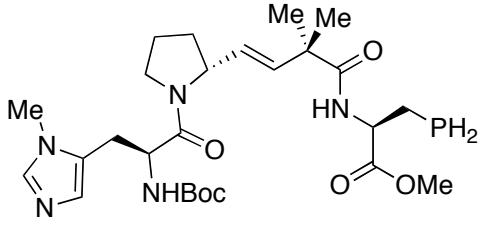
Scheme 25: Kinetic resolution of secondary alcohols



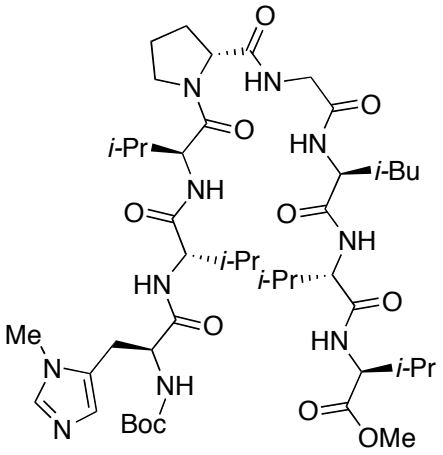
(±) **-83** **84**



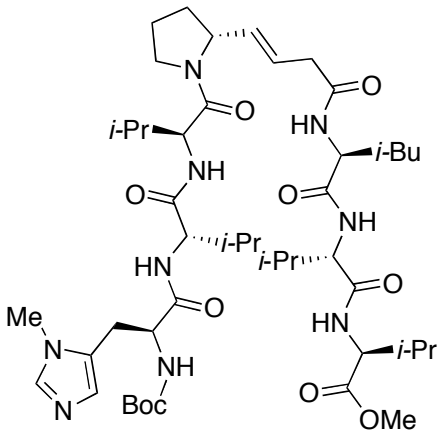
k_{rel}=28



k_{rel}=1



k_{rel}=51



k_{rel}=50

Results from these studies have demonstrated that this interaction is pivotal in providing selectivity for smaller pentameric peptides; however, that same interaction is not as crucial in the longer octameric peptides. Based on this data, the ability of peptides to interact and differentiate between two enantiomers of an aliphatic substrate (lacking a hydrogen bond donor or acceptor) is brought to light. Performing kinetic resolutions on aliphatic secondary alcohols presents a system allowing for this type of study. Along with providing interesting substrates to study, a reliable method for the preparation of optically active aliphatic

substrates, which are synthetically relevant intermediates in the synthesis of natural products, would be a significant contribution to synthetic methodology.

3.2 Aliphatic Systems in Nature

The ability of enzymes to selectively bind with small molecules is important for many successful biological processes. While enzymes utilize myriad tools for this process, one of the more prevalent of these is the hydrophobic effect. This interaction is not only thought to play an important role in protein folding but also in substrate recognition. The important role that hydrophobic interactions play may be a reason for the abundance of natural products containing hydrophobic, unfunctionalized, side chains. The ability to synthesize these natural products, along with analogs, would aid in furthering our understanding of biological processes and provide potentially new and powerful therapeutic agents.

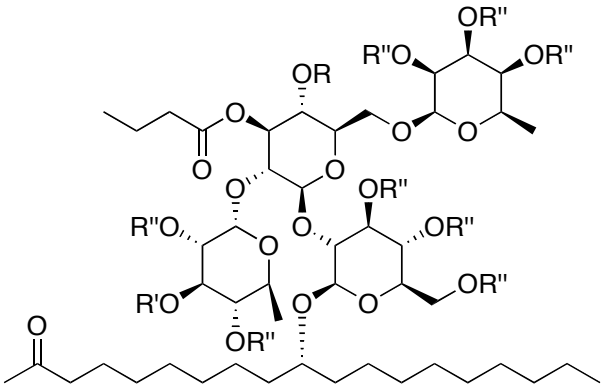
One class of enzymes that bind to aliphatic substrates are aminopeptidases. These enzymes are responsible for the hydrolysis of amino acids from the *N*-terminis of peptides, and are important for cellular functioning. There are two classes of aminopetidases: those that hydrolyze specific amino acids, and those responsible for hydrolyzing hydrophobic residues. Inhibition of amino acid specific methionyl aminopeptidases (MetAP) has been shown to be an effective method of suppressing blood vessel formation and provides potential anticancer activity.[56] Inhibition of aminopeptidases from the hydrophobic hydrolase class could also be effective in preventing the formation of vasculature in tumor cells, along with inhibiting the growth and proliferation of cancer cells. Ustynyuk *et al.* have

[56] Liu, S.; Widom, J.; Kemp, C. W.; Crews, C. M.; Clardy, J. *Science* **1998**, *282*, 1324-1327.

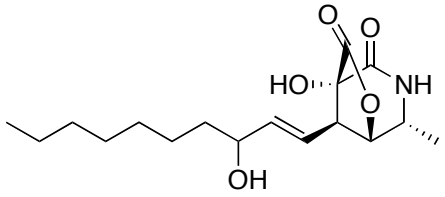
shown that certain aliphatic alcohols are effective at inhibiting this type of aminopeptidase through competitive binding in the hydrophobic pocket.[57]

Apart from being potential anticancer agents, aliphatic sidechains are commonly found in natural products. Recently isolated natural products are the Caminoside family **85** and Awajanomycin (**86**) (Figure 5). Caminoside A (**85A**), isolated from the sponge *Caminus sphaeroconia*, was shown to act as an antimicrobial agent through inhibition of the bacterial type III secretory system.[58] Awajanomycin was isolated from the marine-derived fungus *Acremonium* sp. AWA16-1, and has shown cytotoxic activity against A549 cells (human lung adenocarcinoma).[59]

Figure 5: Caminoside Natural products



	R	R'	R"
Caminoside A (**85A**)	Ac	H	H
Caminoside B (**85B**)	Bu	H	H
Caminoside C (**85C**)	Ac	Bu	H
Caminoside D (**85D**)	Bu	Bu	H



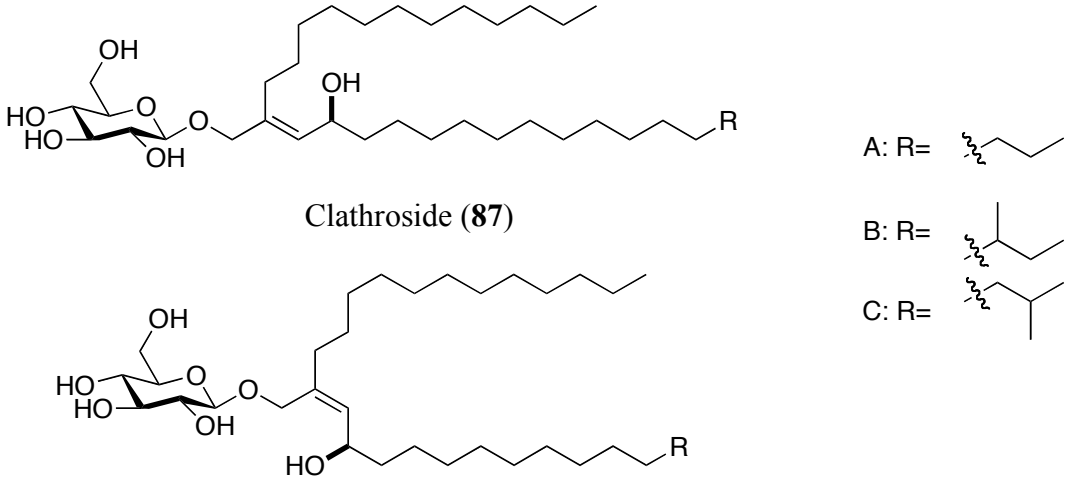
Awajanomycin (**86**)

Another important class of natural products containing aliphatic side chains are glycolipids. These molecules consist of aliphatic alcohols bound to sugars and are prevalent

[57] Ustynyuk, L.; Bennett, B.; Edwards, T.; Holz, R. C.; *Biochemistry* **1999**, *30*, 11433-11439.
[58] Linington, R. G.; Robertson, M.; Gauthier, A.; Finlay, B. B.; Soest, R. v.; Anderson, R. J. *Org. Lett.* **2002**, *4*, 4089-4092.
[59] Jang, J.-H.; Kanoh, K.; Adachi, K.; Shizuri, Y. *J. Nat. Prod.* **2006**, *69*, 1358-1360.

in cell membranes of a significant number of organisms. The immunosuppressive activity of glycolipids isolated from *Plakortis simplex,* known as glycolipids simplexides, has sparked interest in their study.[60] Recently Costantino *et al*. isolated and identified clathrosides A-C (**87**) and isoclathrosides A-C (**88**), which represent a unique family of glycolipids (Figure 6).[61]

Figure 6: Recently isolated glycolipids



Clathroside (**87**)

isoclathrosides (**88**)

3.3 Production of Enantiomerically Pure Aliphatic Substrates

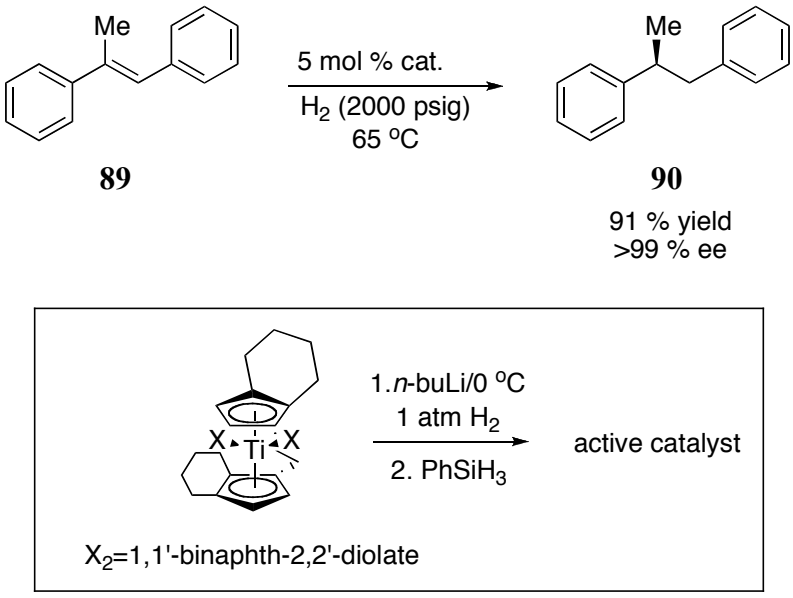
While aliphatic sidechains are prevalent in several natural products, the ability to prepare them in optically pure form provides a significant challenge in organic chemistry. The lack of methodology for the preparation of optically active aliphatic chains is due in part

[60] Costantino, V.; Fattorusso, E.; Mangoni, A.; M. Di Rosa, M.; Ianaro, A. *Bioorg. Med. Chem Lett.* **1999**, *9*, 271-276.
[61] Costantino, V.; Fattorusso, E.; Imperatore, C.; Mangoni, A. *J. Nat. Prod.* **2006,** *69*, 73-78.

to the fact that most chiral catalysts depend on heteroatom functionality for substrate recognition and differentiation.[62]

Asymmetric hydrogenation has shown promise in preparing optically active aliphatic substrates. One of the first examples in this area is the work done by Buchwald in the hydrogenation of "largely unfunctionalized" substrates.[63] Although these early examples deal with substrates containing aromatic substituents, they still provide groundbreaking advances in asymmetric synthesis. In this work, a titanocene pre-catalyst is utilized to achieve high levels of enantioselectivity in the hydrogenation of tri-substituted olefins (Scheme 26).[64]

Scheme 26: Enantioselective hydrogenation of trisubstituted olefins

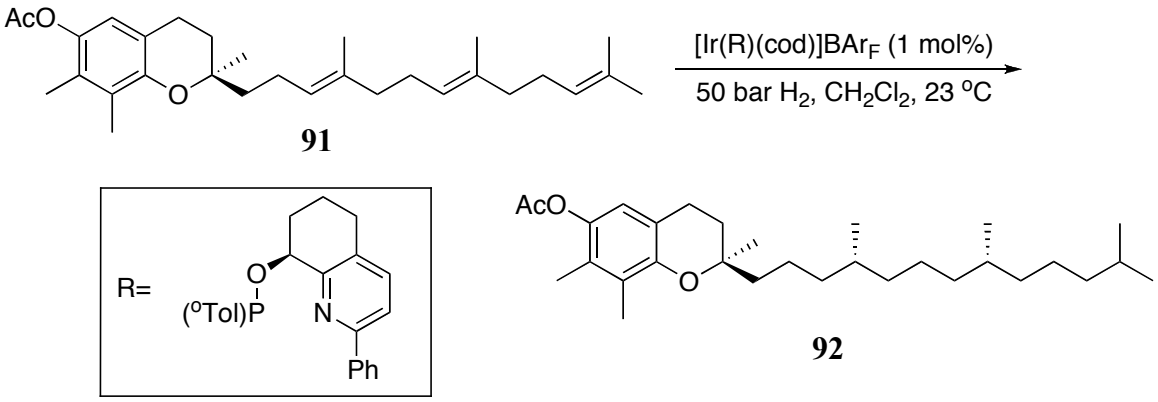


Recently, Pfaltz *et al.* reported the ability of an iridium metal complex to perform asymmetric hydrogenations on olefins devoid of heteroatoms. This represents a major

[62] Willis M. *Science*, **2006**, *311*, 619-620.
[63] Xiuhua, C.; Burgess, K. *Chem. Rev.* **2005**, *105*, 3272-3296.
[64] Broene, R. D.; Buchwald, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 12569-12570.

achievement as the first example of a successful enantioselective hydrogenation of a truly unfunctionalized substrate, as demonstrated in the hydrogenation of γ-tocotrienyl acetate (**91**), a main component of vitamin E (Scheme 27).[65] With the optimized catalyst, great enantio- and diastereoselectivity was observed, giving the product in >98% optical purity with >99% conversion. This catalytic system provides a method for installing two stereocenters in one step, as opposed to the multi-step methods previously required for the preparation of vitamin E analogs.

Scheme 27: Asymmetric hydrogenation of unfunctionalized olefins



3.4 Initial Results for the Kinetic Resolution of 2-Pentanol (93)

Expanding on the limited success observed with β-turn-containing peptides in the kinetic resolution of 2-butanol (k_{rel}=4.0)[66] a selection of β-turn peptides were screened in the kinetic resolution of 2-pentanol. Coupling the success of pentameric peptides in the desymmetrization of glycerol (**61**) and 2-hydroxymethyl cyclopent-2-enone (**76**), focus was concentrated on pentameric peptides. For the initial screen, 8 pentameric peptides with either

[65] Bell, S.; Wustenberg, B.; Kaiser, S.; Menges, F.; Netscher, T.; Pfaltz, A. *Science*, **2006**, *311*, 642-644.
[66] (a) Copeland, G. T.; Miller, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 6496-6502. (b) Blank, J. T.; Guerin, D. J. Miller, S. J. *Org. Lett.* **2000,** *2*, 1247-1249.

D-proline or D-pipecolinic acid in the *i+1* position were screened. The reaction was conducted at room temperature with one equivalent of Hunig's base and 5 mol % catalyst in methylene chloride (Scheme 28, Table 5).

Scheme 28: Kinetic Resolution of 2-pentanol (**93**)

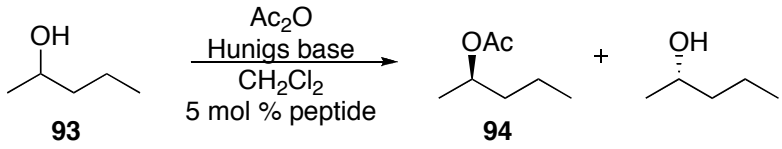


Table 5: Initial Screen in the Kinetic resolution of 2-pentanol (**93**)

entry	Peptide	Conversion*	ee*
1	PMH-ProD-HPhe-Phe-PheD	20	40
2	PMH-ProD-Ile-Phe-PheD	12	24
3	PMH-ProD-Val-Phe-PheD	8	19
4	PMH-PipD-Aib-Trp(Boc)-PheD	6	10
5	PMH-PipD-Asn(Trt)-Phe-PheD	18	50
6	PMH-PipD-Cha-Phe-PheD	13	15
7	PMH-PipD-HPhe-Phe-PheD	14	29
8	PMH-Thr(tBu)-ValD-His(trt)-PheD-ValD-Thr(tBu)-Ile	7	-15
9	PMH-PipD-Sp6-Phe-PheD	10	14

*Crude conversions and ee's of the product were determined by chiral gas chromatography
**Reactions run at -50 ^{o}C with 0.4 eq of Ac_2O, 1 eq of base and 5 mol% catalyst

3.5 Conclusion

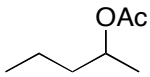
Initial results in the kinetic resolution of 2-pentanol (**93**) indicate the potential for peptides to perform kinetic resolutions on aliphatic alcohols. As observed in this screen, conversion for the reaction was low, indicating lower reactivity for secondary alcohols. Further optimization of the reaction through increasing the temperature or time of the reaction is necessary for increasing the efficiency of the reaction. The volatility of both the starting material and product is also problematic in determining accurately the conversion and enantioselectivity of each catalyst. Drawing on some of the previous work with the peptides, it was also hypothesized that less polar solvents would help to provide a more rigid secondary

structure of the peptide, thus leading to higher enantioselectivites. With this in mind, the next step for the optimization of these reaction conditions would be to investigate the selectivity and reactivity in a variety of solvents such as ether, pentane, or hexane.

After reaction conditions are optimized, a logical step for this project would be a screen involving a variety of octameric peptides containing a β-turn secondary structure. Along with this screen, it would be interesting to see if a pentameric peptide could be optimized to give good selectivity as well. Interestingly, the initial data for this project looks promising and lends itself to the possibility of finding effective catalyst, that could be used for the kinetic resolution of aliphatic alcohols.

3.6 Experimental

Typical procedure for the acylation of 2-pentanol (**93**)



2-Pentanol (**93**) was dissolved in CH_2Cl_2 and Hünig's base, DMAP, and acetic anhydride are added. The reaction was stirred at r.t. and monitored by GC. Upon completion, the reaction was run through a plug of silica gel and eluted with ethyl ether. Analysis of the product was done using chiral GC. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.92 (m, 1 H), 2.03 (s, 3 H), 1.57 (m, 1 H), 1.44 (m, 3 H), 1.21 (d, *J*=6.4 Hz, 3 H), 0.91 (m, 3 H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.7, 71.0, 38.4, 21.7, 20.3, 19.0, 14.3 ppm.